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Abstract

Introduction： Cardiovascular diseases are the leading cause of death and disability in the world. Increasing lifespans and aging populations also contribute to an increasing burden due to cardiovascular diseases. However, in China, we are lacking in related elderly population studies as well as a well-designed domestic CV risk score. The objective of this study is to establish a cardiovascular risk score based on a community-dwelling Chinese elderly population, determining the profile of the associated cardiovascular risk factors and target organ damages (TODs), so as to guide later interventions.

Methods and Analysis:

The Northern Shanghai Study is an ongoing prospective community-based study of over 4000 elderly participants. After enrollment, clinical examinations, physical tests, and questionnaire of the participants will be administered at baseline and after every 2 and 5 years. Our tests and examinations include: blood/urine collection, office blood pressure, carotid ultrasonography, echocardiography, pulse wave velocity, pulse wave analysis, four-limb blood pressure, body mass index and waistline. Baseline assessment analysis will be conducted including the target organ damage indicators and the conventional cardiovascular risk factors. Future analysis will be conducted on the basis of the occurrence of future cardiovascular events. Meanwhile, a Northern Shanghai Risk Score will be established, which is based on CV risk factors and TODs.

Ethics and dissemination:

This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board. All participants signed a written consent form.

Registration number: Clinicaltrials.gov Identifier: NCT02368938

Strengths and limitations of this study:

Strengths:

1. This study is one of the largest on-going prospective population study to evaluate hypertensive target organ damages in community-dwelling elderly Chinese, which is authorized and municipally funded with prior registration.
2. This study shows good population consistency of various measurements. A systemic measuring process including a series of hypertensive target organ damages for all the community-dwelling participants is conducted.

Limitations:

This study is restricted to participants over 65 years old, though age will be considered in the analysis.

Background:

Cardiovascular disease (CVD), as an aging-related and chronic disorder, carries a high incidence of morbidity. It is one of the most common and deadliest diseases in the world [1, 2]. According to a report from the WHO, cardiovascular disease is responsible for 17.5 million deaths annually worldwide [3]. It was the leading cause of death and reduction on expected lifespan [4]. In 2012, about 3.5 million deaths in China were attributable to CVD, which means there would be a CVD death every 10 s.[5] Among all the disease-associated deaths in China, it was concluded that over 40% of them were due to CVDs.[6]

Hypertension has become a main contributor to CVD [7]. In 2014, a report indicated that the prevalence of hypertension in adults increased from 18.8% in 2002 to 24.4% in 2012 while the control rate of hypertension increased only from 6.1% to about 9.3%[6]. Furthermore, according to a recent large-scale study in China which includes 205,167 men (41.0%) and 295,056 women (59.0%) [8], 32.5% of the cohort participants had hypertension with an overall control rate of only 4.2%. This great challenge is due in part to the absence of a domestic cardiovascular risk score in China, with heavy reliance on the foreign risk scores based on non-Chinese populations.

Given the perniciousness of cardiovascular diseases, a well-designed cardiovascular risk scores is essential to guide prevention and therapy in China [9, 10]. In fact, in U.S. and Europe, many well-known population studies with great professional achievements and mature cardiovascular risk score systems have already been established with great success, such as the Framingham Risk Score and the European SCORE Risk Charts [11, 12]. Those studies pushed the transition from a poor understanding of cardiovascular disease to a more mature one forward.[13]

The current risk scores in the U.S. and Europe are based on a mainly Caucasian general population. However, in China, things would be different. According to the *World Population Aging 2013*, it will take China only 26 years to experience the population aging, which means there is a rapid aging trend in China. Therefore, it would be inappropriate to apply those risk scores directly to Chinese elderly.

In the next 30-year period, from 2010 to 2040, China will see an increase of 15.7% in the proportion of the population aged over 60 years, from 12.4% to 28.1% which is the fastest in the world[14]. In Shanghai, the proportion aged over 60 years is 28.8% (Elderly population and cause of aging monitoring statistics of Shanghai in 2014 Accession Number: http://www.shmzj.gov.cn/Attach/Attaches/201506/20150610104009609.doc). Thus, Shanghai could be representative of the future Chinese population. We therefore selected community-based citizens in Shanghai as our target population. The characteristics and successful countermeasures to CV risk control in this population could be extrapolated to the future Chinese society with exemplary role. This could potentially allow effective interventions to be designed 10-20 years sooner.

As mentioned above, China is lacking in a well-established domestic cardiovascular risk scores system at present, and prevention strategies and treatments for cardiovascular diseases need significant improvement. There is an urgent desire in China to establish a cardiovascular risk score based on Chinese population study, especially for the elderly. So we will perform a systematical framework of CV risk assessment for community-based elderly participants (>65 years old) in the northern Shanghai area. The assessments will include the conventional CV risk factors, target organ damages and related diseases. Our objective is to establish a Chinese CV risk score, the Northern Shanghai Risk Score, to guide future risk assessment and intervention for the elderly in China.

This paper is to describe the design and method plan for this study.

Method

Study design and Sample Size

The Northern Shanghai Study uses a prospective community-based ongoing study design. This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board and conducted under the financial support from the Shanghai municipal government (Grant ID. 2013ZYJB0902). The preliminary sample size is expected to be 3000-4000 participants.

Subject Eligibility Criteria

We selected 10 communities in northern Shanghai area for our enrollment.
To be eligible for the study, the subject must meet the following inclusion criteria: (1) age 65 years old or more; (2) informed consent should be signed voluntarily; (3) local residents from urban communities in the north of Shanghai; (4) available for long-term follow-up. The subject should be excluded, if the individual: (1) diagnosed with serious heart disease (NYHA≥IV) or end stage renal disease (CKD > 4); (2) suffered from cancer or life expectancy is less than 5 years; (3) stroke within 3 months; (4) not willing to participate in the clinical study; (5) have to quit the trial due to other diseases; (6) violate the protocol; (7) lose contact with the laboratory staff.

Recruitment

The recruitment strategies include: (1) posting study recruitment files in the neighborhood committees and community hospitals; (2) According to the health file, community hospitals recruit the potential subjects by telephone; (3) hand out recruitment flyers directly to the potential subjects. Contact number is included in all the recruitment files and flyers. Before data collection, the filed staff will give a brief oral questionnaire according to the inclusion and exclusion criteria. When the eligible individual shows their interests in participating in this study, the individual will be sufficiently informed, and they will sign the consent form. This information is retained in a database with SAS software, version 9.3 (SAS Institute, Cary, NC, USA)

for this study.

Social, Clinical and biological parameters

Information is obtained from the questionnaire including gender, age, educational level, smoking habits, drinking habits, the presence of diabetes, renal insufficiency, and cardiovascular disease. Cardiovascular diseases include chronic heart failure, peripheral vascular disease, hypertension, arrhythmia, and previous cardiovascular event (the presence of history of myocardial infarction (MI) and/or stroke and/or cardiac revascularization with either angioplasty or coronary artery bypass graft (CABG)).

When measuring body height and body weight, the subjects must disrobe and remove shoes, and stand straight. Waist circumference and hip circumference are measured by flexible rule, waistline refers to the smallest waist circumference while the hip circumference refers to the greatest hip circumference. The body mass index is calculated by dividing weight (kg) by height^2 (m^2).

Venous blood sample are obtained after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides are measured by standard methods [15, 16], and Friedewald formula is used to calculate the low-density lipoprotein cholesterol (LDL-c) [17]. Other biological parameters like plasma/urine albumin and creatinine are measured by standard methods at local laboratories. The urine albumin-to-creatinine ratio is also calculated. The samples will be stored at -80°C. Prior to storage, the date, number of vials, and responsible person will be recorded.

Office blood pressure measurement

After an overnight fast, blood pressure of the candidates are measured in the morning with the subjects' bladder empty, free of tobacco or caffeine for at least 30 minutes before the measurement. The blood pressure is measured in the sitting position, after resting for 5 minutes, using semi-automatic oscillometric device (Omron Health Care, Kyoto, Japan), according to the recommendations of the European Society of Hypertension [18]. The averaged values were calculated for further analysis.

Ultrasonography

All the ultrasonography including echocardiography and carotid ultrasonography is performed by an experienced cardiologist, who is unaware of previous results. The measurement is performed by a single sonographer with MyLab 30 CV machine (ESAOTE SpA, Genoa, Italy), according to the American Society of Echocardiography (ASE) recommendations.[19]

The echocardiography is performed in the left decubitus position. Left ventricular internal diameter at end-diastole (LVIDd) and septal (SWTd) and posterior wall thickness at end-diastole (PWTd) are measured directly. The formula: LVM (g) =0.8 × [1.04 × [(LVIDd+ PWTd+ SWTd) ^{3}− (LVIDd) ^{3}]] +0.6 is used to calculated the LV mass,

based on modeling the LV as a prolate ellipse of revolution.[19] The left ventricular ejection fraction (LVEF) is measured by M-mode echocardiography, and the left atrium (LA) size is measured in the parasternal long axis (PSLAX) and apical 4-chambers views. The heart diastolic function is also measured, including the peak E (early diastolic), peak A (late diastolic) velocities and the primary early diastolic velocities (Ea) with the CW Doppler. The primary early diastolic velocities (Ea) use the lateral tissue Doppler signals.

Carotid ultrasonography is evaluated at common carotid arteries of both sides using a 7.5-MHz transducer. Carotid artery intima-media thickness is measured on the left common carotid artery, 2 cm from the bifurcation, and always performed on plaque-free arterial segments. Intima-media thickness is determined from changes of density of the section which is perpendicular to the vessel wall. Common, internal and external carotid arteries are all scanned longitudinally and transversely to determine the presence of plaques. The measuring process is performed by the same sonographer as the echocardiography.

Four-limb blood pressure measurement

Four-limb blood pressures of participants are measured by VP-1000 (Omron Health Care, Kyoto, Japan) automatically, performed by the same staff who is trained but blinded for the exact data of this study. Bilateral ankle brachial index (ABI), the ratio of the ankle SBP divided by the brachial SBP, could be read from the device and the lower ABI is applied for further analysis in the subsequent studies.

Pulse wave velocity

PWV, which can be estimated by the SphygomoCor device (AtCor, Australia), is reasonable to be measured in a defined segment to assess the arterial stiffness.[20] And it is recommended that the arterial stiffness should be determined noninvasively by the measurement of cf-PWV (Class I; Level of Evidence A) as a golden standard [21, 22]. The measurement is performed with applanation tonometry (SphygmoCor, AtCor Medical, Australia), by two trained observers blinded to the other results according to the European Expert Consensus on Arterial Stiffness.[23]

Subjects need to rest quietly in a temperature controlled room for at least 10 minutes prior to the initial pulse pressure waveform measurements. The pulse analysis will be performed with sensors in the right radial, carotid and femoral arteries in a supine position. Recordings were made simultaneously with an ECG signal, which provided an R-timing reference, simultaneously, the delay is estimated and the cf-PWV is calculated by the integral software automatically (m/s). The superficial distance covered by the pulse wave will be taken with a tape from the suprasternal notch to the carotid and femoral arteries at the sensor location. [24] An operator index greater than 80% is considered as a reliable measurement, in which the quality and reproducibility of the tonometry measurements are automatically tested.

Pulse wave analysis (PWA)

PWA, which can be observed on the commonly used device - SphygomoCor device (AtCor, Australia) [25], is a vital tool to estimate central hemodynamic parameters so as to assess the target organ damage with the golden standard of tonometry.[26] SphygmoCor is used to perform the applanation tonometry on radial and carotid arteries with the methodology previously described.[25] After a 10 minute rest in supine position, the brachial BP is obtained with the SphygomoCor device. Then, the tonometric device will record 10s data of radial and carotid pulse waves (PWs), followed by a second measurement of brachial BP. [25] Radial waveform is recorded by one trained and experienced physician with a tonometry-based probe. And the radial and carotid recording are performed with the second tonometric device. Central waveform were estimated by the inbuilt software, automatically, with the help of a generalized transfer function which has already been validated. Eventually, the central waveform were calibrated by the calculated brachial mean and diastolic BP, in order to obtain the central SBP and DBP.

The SphygmoCor device provides a quality index, only PWs with an operator index above 80 are accepted. In order to compare PWs with minimal hemodynamic differences, between measurements done prior to devices, it is only when the brachial systolic and diastolic BP varied by less than 3mmHg that the data would be accepted. As for heart rate (HR), a variation no greater than 5% is accepted.

Electrocardiography

The 12 lead resting electrocardiography is recorded at 25 mm/s and 1 mV/cm standardization with standard equipment after at least 5 minutes. Electrocardiographic QRS wave voltage is detected in this study. Parameters including the voltage of the S wave of the chest lead V1 (SV1), S wave of the lead V3 (SV3), R wave of the lead V5 (RV5), R wave of the lead aVL (RaVL) and the duration of QRS wave. Several indexes to distinguish the left ventricular hypertrophy are as follows: Sokolow-Lyon-Rappaport index (SV1 or SV2+RV5 or RV6$\geqslant$4.0 mv in males and SV1 or SV2+RV5 or RV6$\geqslant$3.5mv in females), Cornell criterion (SV3+RaVL$\geqslant$2.8mv in male and SV3+RaVL $\geqslant$2.8mv in female) and Cornell Product [(SV3+RaVL)$\times$QRS duration $\geqslant$244mv • ms in males and (SV3+RaVL+0.6) $\times$QRS duration$\geqslant$244mv • ms].

Evaluation of peripheral artery involvement

The ankle-brachial index (ABI) is used to evaluate the peripheral artery involvement. [27] Brachial-ankle index and brachial-ankle pulse wave velocity are assessed automatically by in-built software using VP-1000 device (Omron, Japan). This measurement is performed in the morning without coffee or tobacco for at least 8 hours prior to measuring in an ambient temperature of 22-24°C.

Definition of hypertensive target organ damages (TODs)

Generally, asymptomatic hypertensive TODs include cardiac, arterial and renal TODs.

Left ventricular hypertrophy is defined as LVMI ≥ 115 g/m2 (male) or LVMI ≥ 95 g/m2 (female). LV diastolic dysfunction is assessed by E/Ea and other evidence of abnormal LV relaxing and filling, such as enlarged left atrial volume and increased LVM [28]. As for the arterial TODs, they were defined as increased CIMT (CIMT > 0.9 μm) or peripheral artery disease (ABI < 0.9), and chronic kidney diseases (CCR < 60 ml/min/1.73m2) and microalbuminuria (UACR > 30) represented renal TODs. Specifically, we defined diastolic dysfunction as 15 > E/Ea > 8 with any of the follows (LAVI > 40 ml/m2 or LVMI > 149 g/m2 (men) or LVMI ≥ 122 g/m2 (women)) or E/Ea ≥ 15.

Clinical outcome:

The primary outcome is a composite of major adverse cardiovascular events (MACE) including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction or revascularization (PCI or CABG). Nonfatal stroke is defined as the new onset of neurological deficiency symptoms or signs lasting for at least 24 h accompanied by evidence from either cranial CT or MRI. Nonfatal MI is defined by canonical chest pain symptoms and/or characteristic electrocardiographic changes with a rise of either troponin I > 1.0 ng/mL or troponin T > 0.1 ng/mL. Coronary revascularization with either PCI or CABG is defined as a history of either stent implantation (PCI) or coronary artery bypass grafting.

The secondary outcome include: 1) subclinical organ damage which is defined as left ventricular hypertrophy or decreased diastolic function or carotid intima-media thickness and plaques or hardening of the arteries or renal insufficiency (CKD3 period) or urine micro protein increased; 2) new onset cardiovascular or cerebrovascular disease, renal insufficiency with proteinuria and diabetes mellitus.

Baseline Visit and Patient Follow-up

Measure	Time-points		
	Baseline	Every 2 years	Every 5 years
Consent Form	●	●	●
Baseline questionnaire (age, gender, smoking history, family history, medication history, symptoms and signs of HF)	●		●
Follow-up questionnaire (newly onset cardiovascular or cerebrovascular events, kidney disease, DM)		●	●
Height, weight, body mass index (BMI) and waistline	●		●
Four-limbs blood pressure measurement	●		●
Office blood pressure measurement (3 times in a row)	●	●	●
Venous blood biochemical parameters (blood glucose and glycosylated hemoglobin, blood lipid, serum creatinine and uric acid, pro - BNP, homocysteine)	●	●	●

Urinalysis (urine micro-albumin and urine creatinine)	●		●
Blood and/or urine sample collection	●	●	●
Electrocardiogram (rhythm, SV1 + RV5)	●		●
Vascular ultrasonography (bilateral carotid artery IMT)	●		●
Echocardiography (LVM，LAV，LVEF，E/Ea，E/A)	●		●
Determination of arterial elasticity (PWA, PWV)	●		●
Evaluation of peripheral artery involvement	●	●	●
Major adverse cardiovascular events		●	●
Cardiovascular deaths		●	●
All-cause deaths		●	●

Statistical Analytic Approach for Primary Aim

Survival curves are generated by the Cox's proportional hazards regression model and survival among groups will be compared using the log-rank test. Receiver operating characteristic (ROC) curve will be used to evaluate the effect of differentiating the occurrence of MACE by any other risk factors in the subsequent studies. A two-sided significance level of 5% is considered the level of statistical significance. The analyses will be conducted with SAS software, version 9.3 (SAS Institute, Cary, NC, USA)

Data Entry and Management of Data Files

All data are entered into computerized database with SAS software, version 9.3 (SAS Institute, Cary, NC, USA). Values that are out of range or represent errors of faulty logic are avoided by double check. Confidentiality is ensured by assigning each patient a study ID number.

Discussion

So far, the Northern Shanghai Study is one of the largest Chinese domestic population studies. We are aiming at the construction of a Chinese CV risk score to guide the future risk assessments and interventions for the elderly. As the burden from the chronic diseases is growing [9, 10], our study will contribute evidence to elderly CV health by establishing the cardiovascular profile of the Chinese aging population.

Some well-established cardiovascular risk scores from several mature population studies have been running successfully, such as the Framingham Risk Score and the European SCORE Risk Charts [11-13]. In fact, most of them were conducted in the general population focusing on conventional risk factors such as smoking, blood pressure, lipid profile, glucose level etc. However, for the elderly, these relevance and predictability between the conventional risk factors and the clinical outcomes has

been narrowed down, partially as result of the influence of comorbidity on risk factors [29-31].

For the elderly, the long-term accumulated micro-damages from conventional risk factors has been converted into target organ damages (TODs). In this respect, our measurements and assessments for the elderly population would be focused on the TODs instead of just the conventional risk factors. Taking a "70 years old chain smoker" with severe atherosclerosis for example, we prefer to try to reverse, terminate or at least control the process of atherosclerosis (TOD), instead of just advising him to give up his long-term formed smoking. Because, for this patient, the CV risk from smoking has been transferred into severe atherosclerosis. The intervention of smoking cessation would be less beneficial compared to the lipid-lowering therapy. For Chinese elderly, some target organ damages are more likely to be reversible than the inveterate risk factors like smoking. Actually, many asymptomatic TODs have been proved to be modifiable by medications, even in the late stage. For example, the cardiac hypertrophy reversing effect of angiotensin receptor blockade (losartan) has been validated [32]. Therefore, we suggest the transition of the CV risk assessment from conventional risk factors (like age, gender and smoking) to the asymptomatic TODs for the elderly, which might be more compatible with the aging population.

Considering all mentioned above, we propose to establish a CV risk score system based on the TODs, mainly aiming at the elderly. In this way, we can provide a more accurate CV assessment as well as a more effective guidance for treatment and intervention. Meanwhile, we may have chance to provide the Chinese policy-makers and opinion leaders with constructive suggestions regarding effective countermeasures to the national CV burden 10-20 years ahead.

Of note, we select Shanghai, as the representative region. Because the current proportion aged over 60 in Shanghai is 28.8% which is similar to the estimated 28.1% of future China (*Elderly population and cause of aging monitoring statistics of Shanghai in 2014*). During this time, China is going to see the population aging in the following years till 2030.[14]

At the very beginning, this study seeks to show the CV profile of about 4000 participants, determining the cardiovascular risks with clinical indicators of subclinical target organ damage. We will analyze the changing values of the target organ damage indicators at every 2 and 5 years, and it's accompanied by new enrollment each time. Additionally, it is also expected that the subsequent follow-up studies in the Northern Shanghai Study will reveal the feasibility and necessity of establishing the Northern Shanghai Score.

We believe that the CV risk score based on TODs for the elderly can make a better prediction for the future CV events, providing more feasible intervention.

Conclusion

This protocol outlines the design and method of the Northern Shanghai Study. Results coming from this study will be used to construct the Northern Shanghai Risk

Score, so as to guide the future assessments and interventions.

Contributorship statement

Hongwei Ji, Jing Xiong, Shikai Yu, Chen Chi, Ximin Fan, Bin Bai, Yiwu Zhou, Jiadela Teliewubai, Yuyan Lu, Yi Zhang acquired the original data for this study. Yi Zhang and Yawei Xu formulated the methods and designed the protocol. Hongwei Ji, Jing Xiong drafted the manuscript. Henry Xu helped us with writing and language review. All authors contributed to revisions and approved the final version of the manuscript.

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Competing Interests

No competing interests.

Ethics approval

Shanghai Tenth People's Hospital Institutional Review Board.

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The Northern Shanghai Study - Cardiovascular Risk and Its Associated Factors in Chinese elderly: A Study Protocol of a prospective study design

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Abstract

Introduction： Cardiovascular diseases are the leading cause of death and disability in the world. Increasing lifespans and aging populations also contribute to an increasing burden due to cardiovascular diseases. However, in China, we are lacking in related elderly population studies as well as a well-designed domestic CV risk score. The objective of this study is to establish a cardiovascular risk score based on a community-dwelling Chinese elderly population, determining the profile of the associated cardiovascular risk factors and target organ damages (TODs), so as to guide later interventions.

Methods and Analysis:

The Northern Shanghai Study is an ongoing prospective community-based study of over 4000 elderly participants. After enrollment, clinical examinations, physical tests, and questionnaire of the participants will be administered at baseline and after every 2 and 5 years. Our tests and examinations include: blood/urine collection, office blood pressure, carotid ultrasonography, echocardiography, pulse wave velocity, pulse wave analysis, four-limb blood pressure, body mass index and waistline. Baseline assessment analysis will be conducted including the target organ damage indicators and the conventional cardiovascular risk factors. Future analysis will be conducted on the basis of the occurrence of future cardiovascular events. Meanwhile, a Northern Shanghai Risk Score will be established, which is based on CV risk factors and TODs.

Ethics and dissemination:

This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board. All participants signed a written consent form.

Registration number: Clinicaltrials.gov Identifier: NCT02368938

Strengths and limitations of this study:

Strengths:

1. This study is one of the largest on-going prospective population study to evaluate hypertensive target organ damages in community-dwelling elderly Chinese, which is authorized and municipally funded with prior registration.
2. This study shows good population consistency of various measurements. A systemic measuring process including a series of hypertensive target organ damages for all the community-dwelling participants is conducted.

Limitations:

Due to limited conditions, left ventricular ejection fraction (LVEF) is measured by M-mode echocardiography, and we do not have an associated device to measure Speckle tracking, which is a powerful method for quantifying ventricular function.

Background:

Cardiovascular disease (CVD), as an aging-related and chronic disorder, carries a high incidence of morbidity. It is one of the most common and deadliest diseases in the world [1, 2]. According to a report from the WHO, cardiovascular disease is responsible for 17.5 million deaths annually worldwide [3]. It was the leading cause of death and reduction on expected lifespan [4]. In 2012, about 3.5 million deaths in China were attributable to CVD, which means there would be a CVD death every 10 s.[5] Among all the disease-associated deaths in China, it was concluded that over 40% of them were due to CVDs.[6]

Hypertension has become a main contributor to CVD [7]. In 2014, a report indicated that the prevalence of hypertension in adults increased from 18.8% in 2002 to 24.4% in 2012 while the control rate of hypertension increased only from 6.1% to about 9.3%[6]. Furthermore, according to a recent large-scale study in China which includes 205,167 men (41.0%) and 295,056 women (59.0%) [8], 32.5% of the cohort participants had hypertension with an overall control rate of only 4.2%. This great challenge is due in part to the absence of a domestic cardiovascular risk score in China, with heavy reliance on the foreign risk scores based on non-Chinese populations.

Given the perniciousness of cardiovascular diseases, a well-designed cardiovascular risk scores is essential to guide prevention and therapy in China [9, 10]. In fact, in U.S. and Europe, many well-known population studies with great professional achievements and mature cardiovascular risk score systems have already been established with great success, such as the Framingham Risk Score and the European SCORE Risk Charts [11, 12]. Those studies pushed the transition from a poor understanding of cardiovascular disease to a more mature one forward.[13]

The current risk scores in the U.S. and Europe are based on a mainly Caucasian general population. However, in China, things would be different. According to the *World Population Aging 2013*, it will take China only 26 years to experience the population aging, which means there is a rapid aging trend in China. On the other hand, China has seen the most rapid urbanization in history. These two trends will interact in important ways with each other and will have a pronounced effect on population's CV health in China. Therefore, it would be inappropriate to apply those risk scores directly to Chinese elderly.In Shanghai, one of the cities with the highest level of urbanization, the proportion aged over 60 years is 28.8% (Elderly population and cause of aging monitoring statistics of Shanghai in 2014 Accession Number: http://www.shmzj.gov.cn/Attach/Attaches/201506/20150610104009609.doc). Thus, Shanghai could be representative of the future Chinese population. We therefore selected community-based citizens in Shanghai as our target population.

Established cardiovascular risk prediction models are mainly based on the conventional risk factors such as age, sex, blood pressure, cholesterol etc. However, if based only on the conventional risk factors, there is a fall in the predictive abilities of

risk scores in older populations [14]. In the elderly, novel biomarkers are warranted to improve the risk stratification instead of relying on a model that is based only on established risk factors [15].

Hypertensive target organ damage, as an intermediate state between risk factors and clinical CV events, may be a good marker for risk stratification [16]. It might better represent exposure to risk factors than the risk factor itself [17]. Therefore, we would like to add valuable TODs, together with conventional risk factors, into the risk assessment model in the elderly.

The characteristics and successful countermeasures to CV risk control in this population could be extrapolated to the future Chinese society with exemplary role. This could potentially allow effective interventions to be designed 10-20 years sooner.

As mentioned above, China is lacking in a well-established domestic cardiovascular risk scores system at present, and prevention strategies and treatments for cardiovascular diseases need significant improvement. There is an urgent desire in China to establish a cardiovascular risk score based on Chinese population study, especially for the elderly. So we will perform a systematical framework of CV risk assessment for community-based elderly participants (>65 years old) in the northern Shanghai area. The assessments will include the conventional CV risk factors, target organ damages and related diseases. Our objective is to establish a Chinese CV risk score, the Northern Shanghai Risk Score, to guide future risk assessment and intervention for the elderly in China.

This paper is to describe the design and method plan for this study.

Method

Study design and Sample Size

The Northern Shanghai Study uses a prospective community-based ongoing study design. This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board and conducted under the financial support from the Shanghai municipal government (Grant ID. 2013ZYJB0902). The preliminary sample size is expected to be 3000-4000 participants.

Subject Eligibility Criteria

We selected 10 communities in northern Shanghai area for our enrollment.
To be eligible for the study, the subject must meet the following inclusion criteria: (1) age 65 years old or more; (2) informed consent should be signed voluntarily; (3) local residents from urban communities in the north of Shanghai; (4) available for long-term follow-up. The subject should be excluded, if the individual: (1) diagnosed with serious heart disease (NYHA≥IV) or end stage renal disease (CKD ≥ 4); (2) suffered from cancer or life expectancy is less than 5 years; (3) stroke within 3 months; (4) not willing to participate in the clinical study; (5) have to quit the trial due to other diseases; (6) violate the protocol; (7) lose contact with the laboratory

staff.

Recruitment

The recruitment strategies include: (1) posting study recruitment files in the neighborhood committees and community hospitals; (2) According to the health file, community hospitals recruit the potential subjects by telephone; (3) hand out recruitment flyers directly to the potential subjects. Contact number is included in all the recruitment files and flyers. Before data collection, the filed staff will give a brief oral questionnaire according to the inclusion and exclusion criteria. When the eligible individual shows their interests in participating in this study, the individual will be sufficiently informed, and they will sign the consent form. This information is retained in a database with SAS software, version 9.3 (SAS Institute, Cary, NC, USA) for this study.

We have two stage to select study subjects. In the first stage, according to *Elderly population and cause of aging monitoring statistics of Shanghai in 2014*, northern Shanghai region has the largest population of older adults in Shanghai, with a total population of 1.57 million and an elderly proportion of over 19%. Thus, northern Shanghai region including Zhabei district and Putuo district was selected from Shanghai. In the second stage, we use a computer-generated list of communities, and 10 communities were randomly selected for the first-phase enrollment. Other communities in the list will be randomly selected for the later enrollment. According to the inclusion and exclusion criteria, we invite all the eligible older people (over 65 years).

Social, Clinical and biological parameters

Information is obtained from the questionnaire including gender, age, educational level, smoking habits, drinking habits, the presence of diabetes, renal insufficiency, and cardiovascular disease. Cardiovascular diseases include chronic heart failure, peripheral vascular disease, hypertension, arrhythmia, and previous cardiovascular event (the presence of history of myocardial infarction (MI) and/or stroke and/or cardiac revascularization with either angioplasty or coronary artery bypass graft (CABG)).

When measuring body height and body weight, the subjects must disrobe and remove shoes, and stand straight. Waist circumference and hip circumference are measured by flexible rule, waistline refers to the smallest waist circumference while the hip circumference refers to the greatest hip circumference. The body mass index is calculated by dividing weight (kg) by height^2 (m^2).

Venous blood sample are obtained after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides are measured by standard methods [18, 19], and Friedewald formula is used to calculate the low-density lipoprotein cholesterol (LDL-c) [20]. Other biological parameters like plasma/urine albumin and creatinine are measured by standard methods at local laboratories. The urine albumin-to-creatinine ratio is also calculated. The samples will

be stored at -80°C. Prior to storage, the date, number of vials, and responsible person will be recorded.

Office blood pressure measurement

After an overnight fast, blood pressure of the candidates are measured in the morning with the subjects' bladder empty, free of tobacco or caffeine for at least 30 minutes before the measurement. The blood pressure is measured in the sitting position, after resting for 5 minutes, using semi-automatic oscillometric device (Omron Health Care, Kyoto, Japan), according to the recommendations of the European Society of Hypertension [21]. The averaged values were calculated for further analysis.

Ultrasonography

All the ultrasonography including echocardiography and carotid ultrasonography is performed by an experienced cardiologist, who is unaware of previous results. The measurement is performed by a single sonographer with MyLab 30 CV machine (ESAOTE SpA, Genoa, Italy), according to the American Society of Echocardiography (ASE) recommendations.[22]

The echocardiography is performed in the left decubitus position. Left ventricular internal diameter at end-diastole (LVIDd) and septal (SWTd) and posterior wall thickness at end-diastole (PWTd) are measured directly. The formula: LVM (g) =0.8 × [1.04 × [(LVIDd+ PWTd+ SWTd) ^{3}– (LVIDd) ^{3}]] +0.6 is used to calculated the LV mass, based on modeling the LV as a prolate ellipse of revolution.[22] The left ventricular ejection fraction (LVEF) is measured by M-mode echocardiography, and the left atrium (LA) size is measured in the parasternal long axis (PSLAX) and apical 4-chambers views. Left atrial volume is calculated using the ellipse model formula: left atrial volume = π × (SA1 × SA2 × LA) / 6. In this equation, SA1 is the M-mode left atrial dimension in the parasternal short-axis view and SA2 and LA are measurements of short- and long-axes in the apical four chamber view at ventricular end-systole [23]. The heart diastolic function is also measured, including the peak E (early diastolic), peak A (late diastolic) velocities and the primary early diastolic velocities (Ea) with the PW Doppler. The primary early diastolic velocities (Ea) use the lateral tissue Doppler signals.

Carotid ultrasonography is evaluated at common carotid arteries of both sides using a 7.5-MHz transducer. Carotid artery intima-media thickness is measured on the left common carotid artery, 2 cm from the bifurcation, and always performed on plaque-free arterial segments. Intima-media thickness is measured manually. The border is determined from changes of density of the section which is perpendicular to the vessel wall. Common, internal and external carotid arteries are all scanned longitudinally and transversely to determine the presence of plaques. And the plaque is defined as intima–media thickness (IMT) of the internal carotid artery of more than 1.5 mm [24] or a localized echo-structure encroaching into the vessel lumen with the arterial wall above 50% thicker than neighboring sites. The measuring process is

performed by the same sonographer as the echocardiography.

Four-limb blood pressure measurement

Four-limb blood pressures of participants are measured by VP-1000 (Omron Health Care, Kyoto, Japan) automatically, performed by the same staff who is trained but blinded for the exact data of this study. Bilateral ankle brachial index (ABI), the ratio of the ankle SBP divided by the brachial SBP, could be read from the device and the lower ABI is applied for further analysis in the subsequent studies.

Pulse wave velocity

PWV, which can be estimated by the SphygomoCor device (AtCor, Australia), is reasonable to be measured in a defined segment to assess the arterial stiffness.[25] And it is recommended that the arterial stiffness should be determined noninvasively by the measurement of cf-PWV (Class I; Level of Evidence A) as a golden standard [26, 27]. The measurement is performed with applanation tonometry (SphygmoCor, AtCor Medical, Australia), by two trained observers blinded to the other results according to the European Expert Consensus on Arterial Stiffness.[28]

Subjects need to rest quietly in a temperature controlled room for at least 10 minutes prior to the initial pulse pressure waveform measurements. The pulse analysis will be performed with sensors in the right radial, carotid and femoral arteries in a supine position. Recordings were made simultaneously with an ECG signal, which provided an R-timing reference, simultaneously, the delay is estimated and the cf-PWV is calculated by the integral software automatically (m/s). The superficial distance covered by the pulse wave will be taken with a tape from the suprasternal notch to the carotid and femoral arteries at the sensor location. [29] An operator index greater than 80% is considered as a reliable measurement, in which the quality and reproducibility of the tonometry measurements are automatically tested.

Pulse wave analysis (PWA)

PWA, which can be observed on the commonly used device - SphygomoCor device (AtCor, Australia) [30], is a vital tool to estimate central hemodynamic parameters so as to assess the target organ damage with the golden standard of tonometry.[31] SphygmoCor is used to perform the applanation tonometry on radial and carotid arteries with the methodology previously described.[30] After a 10 minute rest in supine position, the brachial BP is obtained with the SphygomoCor device. Then, the tonometric device will record 10s data of radial and carotid pulse waves (PWs), followed by a second measurement of brachial BP. [30] Radial waveform is recorded by one trained and experienced physician with a tonometry-based probe. And the radial and carotid recording are performed with the second tonometric device. Central waveform were estimated by the inbuilt software, automatically, with the help of a generalized transfer function which has already been validated. Eventually, the central waveform were calibrated by the calculated brachial mean and diastolic

BP, in order to obtain the central SBP and DBP.

The SphygmoCor device provides a quality index, only PWs with an operator index above 80 are accepted. In order to compare PWs with minimal hemodynamic differences, between measurements done prior to devices, it is only when the brachial systolic and diastolic BP varied by less than 3mmHg that the data would be accepted. As for heart rate (HR), a variation no greater than 5% is accepted.

Electrocardiography

The 12 lead resting electrocardiography is recorded at 25 mm/s and 1 mV/cm standardization with standard equipment after at least 5 minutes. Electrocardiographic QRS wave voltage is detected in this study. Parameters including the voltage of the S wave of the chest lead V1 (SV1), S wave of the lead V3 (SV3), R wave of the lead V5 (RV5), R wave of the lead aVL (RaVL) and the duration of QRS wave. Several indexes to distinguish the left ventricular hypertrophy are as follows: Sokolow-Lyon-Rappaport index (SV1 or SV2+RV5 or RV6≥4.0 mv in males and SV1 or SV2+RV5 or RV6≥3.5mv in females), Cornell criterion (SV3+RaVL≥2.8mv in male and SV3+RaVL ≥2.8mv in female) and Cornell Product [(SV3+RaVL)×QRS duration ≥244mv • ms in males and (SV3+RaVL+0.6) ×QRS duration≥244mv • ms].

Evaluation of peripheral artery involvement

The ankle-brachial index (ABI) is used to evaluate the peripheral artery involvement. [32] Brachial-ankle index and brachial-ankle pulse wave velocity are assessed automatically by in-built software using VP-1000 device (Omron, Japan). This measurement is performed in the morning without coffee or tobacco for at least 8 hours prior to measuring in an ambient temperature of 22-24°C.

Definition of hypertensive target organ damages (TODs)

Generally, asymptomatic hypertensive TODs include cardiac, arterial and renal TODs. Left ventricular hypertrophy is defined as LVMI ≥ 115 g/m2 (male) or LVMI ≥ 95 g/m2 (female). LV diastolic dysfunction is assessed by E/Ea and other evidence of abnormal LV relaxing and filling, such as enlarged left atrial volume and increased LVM [33]. As for the arterial TODs, they were defined as increased CIMT (CIMT > 0.9 mm) or peripheral artery disease (ABI < 0.9), and chronic kidney diseases (CCR < 60 ml/min/1.73m2) and microalbuminuria (UACR > 30) represented renal TODs. Specifically, LV diastolic dysfunction is present when ≥3 listed variables meet these cutoff values (septal e′, 7 cm/sec, lateral e′, 10 cm/sec, average E/e′ ratio, 14, LA volume index, 34 mL/m2) [34].

Clinical outcome:

The primary outcome is a composite of major adverse cardiovascular events (MACE) including cardiovascular death, nonfatal stroke, nonfatal myocardial infarction or revascularization (PCI or CABG). Nonfatal stroke is defined as the new onset of neurological deficiency symptoms or signs lasting for at least 24 h accompanied by

evidence from either cranial CT or MRI. Nonfatal MI is defined by canonical chest pain symptoms and/or characteristic electrocardiographic changes with a rise of either troponin I > 1.0 ng/mL or troponin T > 0.1 ng/mL. Coronary revascularization with either PCI or CABG is defined as a history of either stent implantation (PCI) or coronary artery bypass grafting. A death diagnosis was made on the basis of a death certificate given by our hospital or others'. The endpoint was a combination of questionnaire, dropping-in follow-up and review of the computerized medical records of clinic visits and hospitalizations, conducted by a blinded end-point evaluating committee.

The secondary outcome include: 1) subclinical organ damage which is defined as left ventricular hypertrophy or decreased diastolic function or carotid intima-media thickness and plaques or hardening of the arteries or renal insufficiency (CKD3 period) or urine micro protein increased; 2) new onset cardiovascular or cerebrovascular disease (new onset hypertension, transient ischemic attack, etc.), renal insufficiency with proteinuria and diabetes mellitus.

Baseline Visit and Patient Follow-up

	Time-points		
Measure	Baseline	Every 2 years	Every 5 years
Consent Form	●	●	●
Baseline questionnaire (age, gender, smoking history, family history, medication history, symptoms and signs of HF)	●		●
Follow-up questionnaire (newly onset cardiovascular or cerebrovascular events, kidney disease, DM)		●	●
Height, weight, body mass index (BMI) and waistline	●		●
Four-limbs blood pressure measurement	●		●
Office blood pressure measurement (3 times in a row)	●	●	●
Venous blood biochemical parameters (blood glucose and glycosylated hemoglobin, blood lipid, serum creatinine and uric acid, pro - BNP, homocysteine)	●	●	●
Urinalysis (urine micro-albumin and urine creatinine)	●		●
Blood and/or urine sample collection	●	●	●
Electrocardiogram (rhythm, SV1 + RV5)	●		●
Vascular ultrasonography (bilateral carotid artery IMT)	●		●
Echocardiography (LVM，LAV，LVEF，E/Ea，E/A)	●		●
Determination of arterial elasticity (PWA, PWV)	●		●
Evaluation of peripheral artery involvement	●	●	●

Major adverse cardiovascular events	●	●
Cardiovascular deaths	●	●
All-cause deaths	●	●

Statistical Analytic Approach for Primary Aim

Survival curves are generated by the Cox's proportional hazards regression model and survival among groups will be compared using the log-rank test. Receiver operating characteristic (ROC) curve will be used to evaluate the effect of differentiating the occurrence of MACE by any other risk factors in the subsequent studies. A two-sided significance level of 5% is considered the level of statistical significance. The analyses will be conducted with SAS software, version 9.3 (SAS Institute, Cary, NC, USA)

Development of the risk score at baseline and follow-up

Individuals will be randomly selected to be exploratory and validation set. The score will be created on the exploratory set and tested on the validation set. Risk factors including hypertensive target organ damages and clinically known conventional risk factors were selected. The hypertensive target organ damages with predictable value for cardiovascular events (CVE) were left ventricular hypertrophy, arterial stiffening, carotid hypertrophy, lower limb atherosclerosis, micro-albuminuria and renal function decline (CKD≥2). And the conventional risk factors for CVE were age, gender, smoking, obesity, diabetes, hypertension, blood glucose profile and lipid profile. The independent variables were defined and categorized as following: Left ventricular hypertrophy: left ventricular mass index >115g/m2 for male and >95g/m2 for female; Arterial stiffening: carotid-femoral pulse wave velocity (cf-PWV)>12m/s; Carotid hypertrophy: intima-media thickness (IMT) >=0.9mm; Lower limb atherosclerosis: ankle-brachial index (ABI) <=0.9; Micro-albuminuria: urine albumin to creatinine ratio (UACR) >30mg/mmol; Renal function decline: stage 2 CKD: eGFR 60–89 ml/min/ 1.73m2 (MDRD); Stage 3 or more CKD: eGFR <60 ml/min/1.73m2 (MDRD); Age were categorized into two groups: 65-80 years and over 80 years; Obesity: BMI⩾28.0 kg/m2. To estimate significant predictors of CVE, univariate analyses were performed. In principle, only parameters with inflated coefficients are entered into the model. At baseline, considering that TODs are the basics of this model, multiple logistic regression (MLR) was used to calculate β-coefficients of risk factors for CVE and to compare coefficients between TODs and conventional risk factors. Considering CVE as the dependent variable, variables significant at 5% were included in MLR with stepwise backward elimination [35]. At follow-up, the β coefficient in the Cox regression of each independent prognostic variable will be modified into an integral number to construct a prognostic score model (i.e., exp (β) = HR) [36]. P value≤0.05 was considered significant. In the scoring system, based on the magnitude of its regression coefficient, points will be assigned to each variable. Finally, by adding the

score for each variable in the risk model, a sum score will be calculated for each participant. A receiver operating characteristic (ROC) curve and area under the curve (AUC) will be produced to stratify patients at a high risk of CVE. Sensitivity and specificity were calculated for each cut-off score. We take the cut-off score with a maximum Youden index as the optimum.

Validation of the risk score

As individuals were randomly selected to be exploratory and validation set, the performance of the risk score will be evaluated in the validation set as well as the entire sample. The predictive performance of the risk score will be evaluated with the AUCs in ROC curves, including sensitivity and specificity. During the evaluation, net reclassification indices (NRI) will be used to measuring the improvement of risk estimation by classifying individuals to a more correct category [37]. Furthermore, the proportion of individuals who have a score above the optimal cutoff value in the risk score will be compared with the individuals with a low risk score.

Data Entry and Management of Data Files

All data are entered into computerized database with SAS software, version 9.3 (SAS Institute, Cary, NC, USA). Values that are out of range or represent errors of faulty logic are avoided by double check. Confidentiality is ensured by assigning each patient a study ID number.

Discussion

So far, the Northern Shanghai Study is one of the largest Chinese domestic population studies. We are aiming at the construction of a Chinese CV risk score to guide the future risk assessments and interventions for the elderly. As the burden from the chronic diseases is growing [9, 10], our study will contribute evidence to elderly CV health by establishing the cardiovascular profile of the Chinese aging population.

In literature, performances of risk predictive models were different in different populations and settings [38]. Though the ability to predict occurrence of future events in old persons has been studied, there is few study that has published a risk estimation system which can be used to calculate risks in this age group in clinical practice [39].

Some well-established cardiovascular risk scores from several mature population studies have been running successfully, such as the Framingham Risk Score and the European SCORE Risk Charts [11-13]. In fact, most of them were conducted in the general population focusing on conventional risk factors such as smoking, blood pressure, lipid profile, glucose level etc. However, for the elderly, the long-term exposure and accumulated micro-damages from conventional risk factors has been converted into target organ damages (TODs). In this respect, just considering the conventional risk factors in the risk assessment strategy for the elderly may be

inadequate [39].

Taking a “70 years old chain smoker” with severe atherosclerosis for example, we prefer to try to reverse, terminate or at least control the process of atherosclerosis (TOD), instead of just advising him to give up his long-term formed smoking. Because, for this patient, the CV risk from long-term exposure to smoking has been transferred into severe atherosclerosis. The intervention of smoking cessation would be less beneficial compared to the lipid-lowering therapy. For Chinese elderly, some target organ damages are more likely to be reversible than the inveterate risk factors like smoking. Actually, many asymptomatic TODs have been proved to be modifiable by medications, even in the late stage. For example, the cardiac hypertrophy reversing effect of angiotensin receptor blockade (losartan) has been validated [40]. Therefore, we suggest the transition of the CV risk assessment from conventional risk factors (like age, gender and smoking) to the asymptomatic TODs for the elderly, which might be more compatible with the aging population.

Considering all mentioned above, we propose to establish a CV risk score system based on the TODs, mainly aiming at the elderly. In this way, we can provide a more accurate CV assessment as well as a more effective guidance for treatment and intervention. Meanwhile, we may have chance to provide the Chinese policy-makers and opinion leaders with constructive suggestions regarding effective countermeasures to the national CV burden 10-20 years ahead.

Of note, we select Shanghai, as the representative region. Because the current proportion aged over 60 in Shanghai is 28.8% which is similar to the estimated 28.1% of future China (*Elderly population and cause of aging monitoring statistics of Shanghai in 2014*). During this time, China is going to see the population aging in the following years till 2030.[41]

At the very beginning, this study seeks to show the CV profile of about 4000 participants, determining the cardiovascular risks with clinical indicators of subclinical target organ damage. We will analyze the changing values of the target organ damage indicators at every 2 and 5 years, and it’s accompanied by new enrollment each time. Additionally, it is also expected that the subsequent follow-up studies in the Northern Shanghai Study will reveal the feasibility and necessity of establishing the Northern Shanghai Score.

We believe that the CV risk score based on TODs for the elderly can make a better prediction for the future CV events, providing more feasible intervention.

Conclusion

This protocol outlines the design and method of the Northern Shanghai Study. Results coming from this study will be used to construct the Northern Shanghai Risk Score, so as to guide the future assessments and interventions.

Contributorship statement

Hongwei Ji, Jing Xiong, Shikai Yu, Chen Chi, Ximin Fan, Bin Bai, Yiwu Zhou, Jiadela Teliewubai, Yuyan Lu, Yi Zhang acquired the original data for this study. Yi Zhang and

Yawei Xu formulated the methods and designed the protocol. Hongwei Ji, Jing Xiong drafted the manuscript. Henry Xu helped us with writing and language review. All authors contributed to revisions and approved the final version of the manuscript.

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Competing Interests

No competing interests.

Ethics approval

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The Northern Shanghai Study - Cardiovascular Risk and Its Associated Factors in Chinese elderly: A Study Protocol of a prospective study design

By

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Abstract

Introduction： Cardiovascular diseases are the leading cause of death and disability in the world. Increasing lifespans and aging populations also contribute to an increasing cardiovascular burden. However, in China, there were few well-designed cohort studies focusing on the elderly population, let alone an established cardiovascular risk score. The objective of this study is to establish a cardiovascular risk score based on a community-dwelling Chinese elderly population, determining the profile of the associated cardiovascular risk factors and target organ damages (TODs), so as to guide the later intervention.

Methods and Analysis:

The Northern Shanghai Study is an ongoing prospective community-based study. After enrollment, clinical examination, anthropometric measurement, and questionnaire will be administered on each participant at baseline and after every 2 years in the follow-up. Our tests and examinations include: blood/urine sample and biochemical measurements, office blood pressure recording, carotid ultrasonograph, echocardiograph, pulse wave velocity, pulse wave analysis, four-limb blood pressure recording, body mass index and etc. Baseline measurement will also include the assessments on target organ damages and the conventional cardiovascular risk factors. In the follow-up, incidence of cardiovascular events and mortality will be recorded. The Northern Shanghai Risk Score will be calculated, with considerations on both cardiovascular risk factors and TODs.

Ethics and dissemination:

This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board. All participants signed a written consent form.

Registration number: Clinicaltrials.gov Identifier: NCT02368938

Strengths and limitations of this study:

Strengths:

1. This study is one of the largest on-going prospective population study to evaluate target organ damages in community-dwelling elderly Chinese, which is authorized and funded by the Shanghai municipal government.
2. A systematic framework of cardiovascular risk survey was conducted, with considerations on conventional cardiovascular risk factors, asymptomatic target organ damages, cardiovascular diseases, future events and mortality.

Limitations:

1. Left ventricular ejection fraction (LVEF) was measured by the M-mode echocardiograph, but not by the Simpson's method.
2. The risk score is based on the elderly participants, which is already at significant risk due to their old age. However, collected data and the later risk score can also be used for validation in younger cohorts.
3. Some measurements in this study need highly specialized equipment, which is hard to scale to a larger population.

Background:

Cardiovascular diseases (CVDs), as aging-related and chronic disorders, carry a high morbidity. It is one of the most common and deadliest diseases in the world [1, 2]. According to a report from the WHO, CVD is responsible for 17.5 million deaths annually worldwide [3]. It was the leading cause of death and the reduction in human's expected lifespan [4]. In 2012, about 3.5 million deaths in China were attributable to CVDs, which means there would be a CVD death every 10 s in China [5]. Among all the disease-associated deaths in China, it was concluded that over 40% of them were due to CVDs [6].

Hypertension is considered as the major contributor to CVDs [7]. A report indicated that the prevalence of hypertension in Chinese adults increased from 18.8% in 2002 to 24.4% in 2012, while the control rate increased only from 6.1% to 9.3% [6]. Furthermore, according to a recent large-scale survey in China with 205,167 men (41.0%) and 295,056 women (59.0%) [8], 32.5% of the cohort participants had hypertension with an overall control rate of only 4.2%. This great challenge is due in part to the absence of a domestic cardiovascular risk score in China.

Given the perniciousness of CVDs, an established cardiovascular risk score is essential to guide prevention and therapy in China [9, 10]. In fact, in U.S. and Europe, many well-known population studies with great professional achievements were conducted, and some mature cardiovascular risk score systems have already been established and applied efficiently, such as the Framingham Risk Score and the European SCORE Risk Charts [11, 12]. Those studies pushed the transition from a poor understanding of CVDs to a more mature one forward [13].

The current risk scores in the U.S. and Europe are based on a mainly Caucasian general population. However, in China, things would be different. According to the *World Population Aging 2013*, it will take China only 26 years to experience the population aging, which means there is a rapid aging trend in China. On the other hand, China also had the most rapid urbanization in history. These two trends will interact in important ways with each other and will have a profound effect on Chinese CV health. Therefore, it would be inappropriate to apply those risk scores directly in the Chinese elderly. In Shanghai, the biggest urbanized city in China, the proportion aged over 60 years is 28.8% (*Elderly population and cause of aging monitoring statistics of Shanghai in 2014* Accession Number: http://www.shmzj.gov.cn/Attach/Attaches/201506/20150610104009609.doc). In this respect, Shanghai could be a good representative of the future Chinese population, with the deep urbanization and the geriatric population. We therefore selected community-based citizens in Shanghai as our target population. The characteristics and successful experience on the CV risk control in this Shanghai geriatric population, acting as an exemplary role, could be extrapolated to the future Chinese society. It means that, effective interventions for the future Chinese would be designed 10-20 years sooner.

Established cardiovascular risk prediction models are mainly based on the conventional risk factors such as age, sex, blood pressure, cholesterol, etc. However, if based only on the conventional risk factors, there is a fall in the predictive abilities of future risk in the older population [14]. In the elderly, novel biomarkers are warranted to improve the risk stratification instead of relying on a model that is based only on established risk factors [15].

Asymptomatic target organ damage (TOD), as an intermediate state between risk factors and clinical events, may be a good marker for risk stratification in the elderly [16]. It might better represent exposure to risk factors than the risk factor itself [17]. Therefore, we would like to add valuable TODs, together with conventional risk factors, into the risk assessment model in the elderly.

As mentioned above, China is lacking in a well-established domestic cardiovascular risk score system at present, and prevention strategies as well as treatments for CVDs need significant improvement. There is an urgent desire in China to establish a cardiovascular risk score based on Chinese population study, especially for the elderly. So we will perform a systematical framework of CV risk assessment for community-based elderly participants (>65 years old) in the northern Shanghai area. The assessments include conventional CV risk factors, target organ damages and related diseases. Our objective is to establish a Chinese CV risk score, the Northern Shanghai Risk Score, to guide future risk assessments and interventions for the elderly in China.

This paper is to describe the design and method plan for this study.

Method

Study design and Sample Size

The Northern Shanghai Study is a prospective community-based ongoing study. This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board and was conducted under the financial support from the Shanghai municipal government (Grant ID. 2013ZYJB0902 and 15GWZK1002). The preliminary sample size is expected to be 3000-4000 participants.

Subject Eligibility Criteria

The inclusion criteria include: (1) age 65 years old or more; (2) informed consent should be signed voluntarily; (3) local residents from communities in the northern Shanghai; (4) available for long-term follow-up. The subject should be excluded, if the individual: (1) was diagnosed with serious heart disease (NYHA≥IV) or end stage renal disease (CKD ≥ 4 stage); (2) suffered from cancer or his/her life expectancy is less than 5 years; (3) had stroke within 3 months; (4) is not willing to participate in the clinical study; (5) has to quit the trial due to other diseases; (6) violates the protocol; (7) loses contact with the laboratory staff.

Recruitment

First, according to *Elderly population and cause of aging monitoring statistics of Shanghai in 2014*, northern Shanghai region has the largest population of elderly adults in Shanghai, with a total population of 1.57 million and an elderly proportion of over 19%. Thus, northern Shanghai region including Zhabei district and Putuo district was selected from Shanghai. Second, we use a computer-generated list of communities, and 10 communities were randomly selected for the first-phase enrollment. Other communities in the list will be randomly selected for the later enrollment. According to the inclusion and exclusion criteria, we invite all the eligible older people (over 65 years) to participant this study.

The recruitment strategies include: (1) posting study recruitment files in the neighborhood committees and community hospitals; (2) According to the health file, community hospitals recruit the potential subjects by telephone; (3) hand out recruitment flyers directly to the potential subjects. Contact number is included in all the recruitment files and flyers. Before data collection, the filed staff will give a brief oral questionnaire according to the inclusion and exclusion criteria. When the eligible individual shows their interests in participating in this study, the individual will be sufficiently informed, and they will sign the consent form.

Social, Clinical and biological parameters

Information is obtained from the standardized questionnaire including gender, age, education level, smoking habits, drinking habits, history of diabetes, renal insufficiency, and CVD. CVDs include chronic heart failure, peripheral vascular disease, hypertension, arrhythmia, and previous cardiovascular event (the presence of history of myocardial infarction (MI) and/or stroke and/or cardiac revascularization with either angioplasty or coronary artery bypass graft (CABG)).

Subjects must disrobe and remove shoes and stand straight, before their body height and body weight are measured. Waist circumference and hip circumference are measured by flexible rule, with waistline and hipline refering to the smallest waist and the greatest circumferences, respectively. The body mass index is calculated by dividing body weight (kg) with the squared body height (m^2).

Venous blood samples are obtained after an overnight fast. Total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides are measured by standard methods [18, 19], and Friedewald formula is used to calculate the low-density lipoprotein (LDL) cholesterol (LDL-c) [20]. Other biological parameters like plasma/urine albumin and creatinine are measured by standard methods at local laboratories. The urine albumin-to-creatinine ratio (UACR) is also calculated. The serum and urine samples will be stored at -80°C. Prior to storage, the date, number of vials, and responsible person will be recorded.

Office blood pressure measurement

After an overnight fast, brachial blood pressure is measured in the morning with the subjects' bladder empty, free of tobacco or caffeine for at least 30 minutes before the measurement. The blood pressure is measured in the sitting position, after resting for 5 minutes, using semi-automatic oscillometric device (Omron Health Care, Kyoto, Japan), according to the recommendations of the European Society of Hypertension [21]. The average value is calculated for further analysis.

Ultrasonography

All the ultrasonography measurements including echocardiography and carotid ultrasonography are performed by a single experienced cardiologist, who is unaware of previous results. All measurement are performed with MyLab 30 CV machine (ESAOTE SpA, Genoa, Italy), according to the American Society of Echocardiography (ASE) recommendations.[22]

The echocardiography is performed in the left decubitus position. Left ventricular internal diameter at end-diastole (LVIDd) and septal (SWTd) and posterior wall thickness at end-diastole (PWTd) are measured directly. The formula: LVM (g) =0.8 × [1.04 × [(LVIDd+ PWTd+ SWTd) ^{3}– (LVIDd) ^{3}]] +0.6 is used to calculated the LV mass, based on modeling the LV as a prolate ellipse of revolution [22]. The left ventricular ejection fraction (LVEF) is calculated by the Teichholz's formula, and the left atrium (LA) size is measured in the parasternal long axis (PSLAX) and apical 4-chambers views. Left atrial volume is calculated using the ellipse model formula: left atrial volume = π × (SA1 × SA2 × LA) / 6. In this equation, SA1 is the M-mode left atrial dimension in the parasternal short-axis view and SA2 and LA are measurements of short- and long-axes in the apical four chamber view at ventricular end-systole [23]. The heart diastolic function is also measured, including the peak E (early diastolic), peak A (late diastolic) velocities and the primary early diastolic velocities (Ea) with the PW and TDI Doppler. The primary early diastolic velocities (Ea) are measured by the lateral tissue Doppler signals.

Carotid ultrasonography is evaluated at common carotid arteries of both sides using a 7.5-MHz transducer. Carotid artery intima-media thickness (CIMT) is measured on the left common carotid artery, 2 cm from the bifurcation, and is always performed on plaque-free arterial segments. Intima-media thickness is measured manually. The border is determined from changes of density of the section which is perpendicular to the vessel wall. Common, internal and external carotid arteries are all scanned longitudinally and transversely to determine the presence of plaques. And the plaque is defined as intima–media thickness (IMT) of the internal carotid artery of more than 1.5 mm [24] or a localized echo-structure encroaching into the vessel lumen with the arterial wall above 50% thicker than neighboring sites. The measuring process is performed by the same sonographer as the echocardiography.

Four-limb blood pressure measurement

Four-limb blood pressures of participants are measured by VP-1000 (Omron Health Care, Kyoto, Japan) automatically, performed by the trained staff. Bilateral ankle brachial index (ABI), the ratio of the ankle systolic blood pressure (SBP) divided by the brachial SBP, could be read from the device and the lower ABI is applied for further analysis in the subsequent studies.

Pulse wave velocity (PWV)

PWV, which can be estimated by the SphygomoCor device (AtCor, Australia), is measured in a defined segment to assess the arterial stiffness.[25] And it is recommended that the arterial stiffness should be determined noninvasively by the measurement of carotid-femoral PWV (cf-PWV) (Class I; Level of Evidence A) as a golden standard [26, 27]. The measurement is performed with applanation tonometry (SphygmoCor, AtCor Medical, Australia), by two trained observers blinded to the other results according to the European Expert Consensus on Arterial Stiffness [28].

Subjects need to rest quietly in a temperature controlled room for at least 10 minutes prior to the initial pulse pressure waveform measurements. The pulse analysis will be performed with sensors in the right radial, carotid and femoral arteries in a supine position. Recordings were made simultaneously with an ECG signal, which provided an R-timing reference, simultaneously, the delay is estimated and the cf-PWV is calculated by the integral software automatically (m/s). The superficial distance covered by the pulse wave will be taken with a tape from the suprasternal notch to the carotid and femoral arteries at the sensor location [29]. An operator index greater than 80% is considered as a reliable measurement, in which the quality and reproducibility of the tonometry measurements are automatically tested.

Pulse wave analysis (PWA)

PWA, which can be observed on the commonly used device - SphygomoCor device (AtCor, Australia) [30], is to estimate central hemodynamic parameters.[31] SphygmoCor is used to perform the applanation tonometry on radial artery with the methodology previously described [30]. After a 10 minute rest in supine position, the brachial BP is obtained with the SphygomoCor device. Then, radial waveform is recorded by one trained and experienced physician with a tonometry-based probe. Central waveform is estimated by the inbuilt software, automatically, with the help of a validated generalized transfer function. Eventually, the central waveform is calibrated by the calculated brachial mean and diastolic blood pressure (DBP), in order to obtain the central SBP and DBP.

The SphygmoCor device provides a quality index, and only PWs with an operator index above 80 are accepted. The data is accepted only when a variation of heart rate is no greater than 5%.

Electrocardiography

The 12 lead electrocardiograph is recorded at 25 mm/s and 1 mV/cm standardization with standard equipment after at least 5-minute resting. Electrocardiographic QRS wave voltage is detected in this study. Parameters are recorded and calculated, including the voltage of the S wave of the chest lead V1 (SV1), S wave of the lead V3 (SV3), R wave of the lead V5 (RV5), R wave of the lead aVL (RaVL) and the duration of QRS wave. Several indexes to distinguish the left ventricular hypertrophy are as follows: Sokolow-Lyon-Rappaport index (SV1 or SV2+RV5 or RV6≥4.0 mv in male and SV1 or SV2+RV5 or RV6≥3.5mv in female), Cornell criterion (SV3+RaVL≥2.8mv in male and SV3+RaVL ≥2.8mv in female) and Cornell Product [(SV3+RaVL)×QRS duration≥244mv • ms in male and (SV3+RaVL+0.6) ×QRS duration≥244mv • ms in female].

Evaluation of peripheral artery involvement

The ABI is used to evaluate the peripheral artery involvement [32]. Brachial-ankle index and brachial-ankle PWV are assessed automatically by in-built software using VP-1000 device (Omron, Japan). This measurement is performed in the morning without coffee or tobacco for at least 8 hours prior to measuring and in an ambient temperature of 22-24°C.

Definition of TODs

Generally, asymptomatic TODs include cardiac, arterial and renal TODs.
Left ventricular hypertrophy is defined as LVMI ≥ 115 g/m^2 (male) or LVMI ≥ 95 g/m^2 (female) [33]. As for the arterial TODs, they are defined as increased CIMT (CIMT > 0.9 mm) or peripheral artery disease (ABI < 0.9). Chronic kidney diseases (creatinine clearance rate (CCR) < 60 ml/min/1.73m^2) and micro-albuminuria (UACR >30 mg/mmol) represent renal TODs. Specifically, LV diastolic dysfunction is present when ≥3 listed variables meet these cutoff values (septal e' , 7 cm/sec, lateral e' , 10 cm/sec, average E/e' ratio, 14, LA volume index, 34 mL/m2) [34].

Clinical outcome:

The primary outcome is a composite of major adverse cardiovascular events (MACE) including cardiovascular death, non-fatal stroke, non-fatal myocardial infarction or revascularization (PCI or CABG). Non-fatal stroke is defined as the new onset of neurological deficiency symptoms or signs lasting for at least 24 hours accompanied by evidence from either cranial CT or MRI. Non-fatal MI is defined by canonical chest pain symptom and/or characteristic electrocardiographic changes with a rise of either troponin I > 1.0 ng/mL or troponin T > 0.1 ng/mL. Coronary revascularization with either PCI or CABG is defined as a history of either stent implantation (PCI) or coronary artery bypass grafting (CABG). A death diagnosis is identified on the basis of a death certificate given by the related hospital. The endpoint is defined by a combination of questionnaire, dropping-in follow-up and review of the computerized

medical records of clinic visits and hospitalizations, conducted by a blinded end-point evaluating committee.

The secondary outcome include: 1) subclinical organ damage which is defined as left ventricular hypertrophy or decreased diastolic function or increased carotid intima-media thickness and/or the presence of plaque or hardening of the arteries or renal insufficiency (CKD3 period) or increased micro-albuminuria; 2) newly onset cardiovascular or cerebrovascular disease (newly onset hypertension, transient ischemic attack, etc.), renal insufficiency with proteinuria or newly onset diabetes mellitus.

Baseline Visit and Patient Follow-up

Measure	Time-points		
	Baseline	Every 2 years	Every 5 years
Consent Form	●	●	●
Baseline questionnaire (age, gender, smoking history, family history, medication history, symptoms and signs of HF)	●		●
Follow-up questionnaire (newly onset cardiovascular or cerebrovascular events, kidney disease, DM)		●	●
Body height, body weight, body mass index (BMI) and waist circumference and hip circumference	●		●
Four-limb blood pressure measurement	●		●
Office blood pressure measurement (3 times in a row)	●	●	●
Venous blood biochemical parameters (blood glucose, blood lipid profile, serum creatinine and uric acid, pro - BNP, homocysteine)	●	●	●
Urinalysis (urine micro-albumin and urine creatinine)	●		●
Blood and/or urine sample collection	●	●	●
Electrocardiogram (rhythm, SV1 + RV5)	●		●
Vascular ultrasonography (bilateral carotid IMT)	●		●
Echocardiography (LVM，LAV，LVEF，E/Ea，E/A)	●		●
Determination of arterial elasticity (PWA, PWV)	●		●
Evaluation of peripheral artery involvement	●	●	●
Major adverse cardiovascular events		●	●
Cardiovascular deaths		●	●
All-cause deaths		●	●

Statistical Analytic Approach for Primary Aim

Survival curves are generated by the Cox's proportional hazards regression model and survival among groups will be compared using the log-rank test. Receiver operating characteristic (ROC) curve is used to evaluate the effect of influential factors on the occurrence of MACEs. A two-sided significance level of 5% is defined as the level of statistical significance. The analyses are conducted with SAS software, version 9.3 (SAS Institute, Cary, NC, USA)

Development of the risk score at baseline and follow-up

Individuals will be randomly selected to be exploratory and validation set. The score will be created on the exploratory set and tested on the validation set. Risk factors including TODs and conventional risk factors are selected. The TODs with predictable value for cardiovascular events (CVE) are left ventricular hypertrophy, arterial stiffening, carotid hypertrophy, lower limb atherosclerosis, micro-albuminuria and renal function decline [35]. And the conventional risk factors for CVE include age, gender, smoking, obesity, diabetes, hypertension, blood glucose and lipid profile. The independent variables are defined and categorized as following: Left ventricular hypertrophy: left ventricular mass index >115g/m^2 for male and >95g/m^2 for female; Arterial stiffening: cf-PWV>12m/s; Carotid hypertrophy: IMT >=0.9mm; Lower limb atherosclerosis: ABI <=0.9; Micro-albuminuria: UACR >30mg/mmol; Renal function decline: stage 2 CKD: eGFR 60–89 ml/min/ 1.73m^2 (MDRD); Stage 3 or more CKD: eGFR <60 ml/min/1.73m^2 (MDRD); Age is categorized into two groups: 65-80 years and over 80 years; Obesity: BMI⩾28.0 kg/m^2. To estimate significant predictors of CVE, univariate analyses will be performed. In principle, only parameters with inflated coefficients are entered into the model. At baseline, considering that TODs are the basics of this model, multiple logistic regression (MLR) will be used to calculate β-coefficient of risk factors for CVE and to compare coefficients between TODs and conventional risk factors. Considering CVE as the dependent variable, variables significant at 5% will be included in MLR with stepwise backward elimination [36]. At follow-up, the β coefficient in the Cox regression of each independent prognostic variable will be modified into an integral number to construct a prognostic score model (i.e., exp (β) = HR) [37]. P value≤0.05 is considered significant. In the scoring system, based on the magnitude of its regression coefficient, points will be assigned to each variable. Finally, by adding the score for each variable in the risk model, a sum score will be calculated for each participant. A receiver operating characteristic (ROC) curve and area under the curve (AUC) will be assessed to stratify patients at a high risk of CVE. Sensitivity and specificity will be calculated for each cut-off score. The cut-off score with a maximum Youden index will be considered as the optimum.

Validation of the risk score

As individuals are randomly selected to be exploratory and validation set, the performance of the risk score will be evaluated in the validation set as well as the entire sample. The predictive performance of the risk score will be evaluated with the AUCs in ROC curves, including sensitivity and specificity. During the evaluation, net reclassification indices (NRI) will be used to measuring the improvement of risk estimation by classifying individuals to a more correct category [38]. Furthermore, the proportion of individuals who have a score above the optimal cutoff value in the risk score will be compared with those with a low risk score.

Data Entry and Management of Data Files

All data are entered into computerized database with SAS software, version 9.3 (SAS Institute, Cary, NC, USA). Values that are out of range or represent errors of faulty logic are avoided by double check.

Discussion

So far, the Northern Shanghai Study is one of the largest Chinese domestic population studies. We are aimed at building a CV risk score to guide the future risk assessments and interventions for the elderly Chinese. As the burden from the chronic diseases is growing [9, 10], our study will also contribute to Chinese CV health by establishing the cardiovascular profile of the Chinese aging population.

In literature, risk predictive models have been established in various populations and in different settings [39]. Though the ability to predict occurrence of future events in old persons has been studied, there is few study that has published a risk estimation system which can be used to calculate risks in this age group in clinical practice [40].

Some well-established cardiovascular risk scores from famous population studies run successfully, such as the Framingham Risk Score and the European SCORE Risk Charts [11-13]. In fact, most of them were conducted in the general population focusing on conventional risk factors such as smoking, blood pressure, lipid profile, glucose level, etc. However, for the elderly, the long-term exposure and accumulated micro-damages from conventional risk factors has been converted into target organ damages (TODs). In this respect, just considering the conventional risk factors in the risk assessment strategy for the elderly may be inadequate [40].

Taking a “70 years old chain smoker” with severe atherosclerosis for example, we prefer to reverse, terminate or at least control the process of atherosclerosis (TOD), instead of just advising him to quit his long-term formed smoking. Because, for this patient, the CV risk from long-term exposure to smoking has been transferred into severe atherosclerosis. The intervention of smoking cessation would be less beneficial compared to the lipid-lowering therapy. For Chinese elderly, some target organ damages are more likely to be reversible than the inveterate risk factors like

smoking. Actually, many asymptomatic TODs have been proved to be modifiable by medications, even in the late stage. For example, angiotensin receptor blockade (losartan) has been validated for reversing cardiac hypertrophy [41]. Therefore, we suggest the transition of the CV risk assessment from conventional risk factors (like age, gender and smoking) to the combination of asymptomatic TODs and risk factors in the elderly, which might be more compatible with the aging population.

Considering all mentioned above, we propose to establish a CV risk score system based on the TODs and conventional CV risk factors, focusing on the elderly. In this way, we can provide a more accurate CV assessment as well as a more effective guidance for treatment and intervention. Meanwhile, we may have chance to provide the Chinese policy-makers and opinion leaders with constructive suggestions regarding effective countermeasures to the national CV burden.

Of note, we select Shanghai, as the representative region. Because the current proportion aged over 60 in Shanghai is 28.8% which is similar to the estimated 28.1% of future China in 2040 (*Elderly population and cause of aging monitoring statistics of Shanghai in 2014*) [42].

At the baseline analysis, this study seeks to show the CV profile of about 4000 participants, and to determine subclinical target organ damages with conventional cardiovascular risks. We will analyze the change of the target organ damage indicators at every 2 to 5 years, and it's accompanied by new enrollment each time. Additionally, it is also expected that the subsequent follow-up studies in the Northern Shanghai Study will reveal the feasibility and necessity of establishing the Northern Shanghai Score.

We believe that the CV risk score based on TODs and CV risk factors for the elderly Chinese can make a better prediction for the future CV events, providing more feasible intervention.

Conclusion

This protocol outlines the design and method of the Northern Shanghai Study. Results coming from this study will be used to construct the Northern Shanghai Risk Score, so as to guide the future assessments and interventions.

Contributorship statement

Hongwei Ji, Jing Xiong, Shikai Yu, Chen Chi, Ximin Fan, Bin Bai, Yiwu Zhou, Jiadela Teliewubai, Yuyan Lu, Yi Zhang acquired the original data for this study. Yi Zhang and Yawei Xu formulated the methods and designed the protocol. Hongwei Ji, Jing Xiong drafted the manuscript. Henry Xu helped us with writing and language review. All authors contributed to revisions and approved the final version of the manuscript.

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Competing Interests

No competing interests.

Ethics approval

Shanghai Tenth People's Hospital Institutional Review Board.

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