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Northern Shanghai Study II: systematic assessment and management of early organ damage and its role in preventing and reducing cardiovascular risk—protocol of a prospective study

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ABSTRACT

Introduction Cardiovascular diseases are the leading cause of death and disease burden in China. However, there is a lack of prospective cohort studies suitable for evaluating early organ damage and its role in preventing and reducing cardiovascular risk among Chinese residents. This study intends to establish the first database based on the phenotypes of all early structural and functional damage of cardiovascular organs in Chinese population. Moreover, a digital follow-up mechanism will be formed, a prospective population cohort will be established, a biological sample bank for early cardiovascular organ damage will be established, and an intervention and management system for early damage of cardiovascular organs will be explored.

Methods and analysis This study is a prospective cohort study built on the foundation of the Northern Shanghai Study I. People aged 18–75 years are enrolled. After the recruitment, first, corresponding physical measurements and clinical examinations are conducted to collect cardiovascular risk factors and establish the demographic baseline of the study population. Next, the latest equipment is used to evaluate early structural and functional cardiovascular organ damage including heart, macrovessels, microcirculation, renal function and fundus. Meanwhile, the blood, urine, faeces and other biological samples of participants are collected to establish the cardiometabolic and gut microbiota analysis databases. The population is followed up every 2 years. Comprehensive assessment of early organ damage will be used to predict cardiovascular risk, guide people to change lifestyles to achieve early prevention and provide corresponding treatment recommendations.

Ethics and dissemination This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board. All participants signed a written consent form. The results of this study will be disseminated in peer-reviewed journals. Ethics approval: SHYS-IEC-5.0/22k148/P01.

Trial registration number NCT05435898.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to include all early structural and functional damage of cardiovascular organs in Chinese population.
⇒ The intervention for early cardiovascular organ damage is not solely suitable for the elderly who are already at significant risk, but used with people aged 18–75 years, given a trend of cardiovascular diseases becoming more prevalent among the younger population.
⇒ This study necessitates the employment of highly specialised equipment, which is not amenable to scaling up to a larger population.
⇒ The most desirable situation would be to analyse the influence of early organ damage on terminal events among individuals who do not have cardiovascular diseases, our study includes the group with milder cardiovascular diseases.

INTRODUCTION

With the development of social economy and the acceleration of population ageing and urbanisation, the lifestyle of Chinese residents has changed a lot. Unhealthy lifestyles have become increasingly prominent, and the impact of cardiovascular risk factors on residents' health has become more significant. Cardiovascular disease is the leading cause of death and disease burden among urban and rural residents in China,[1] with characteristics of high prevalence, high incidence, high disability rate and high mortality. At present, the number of patients with cardiovascular disease reaches 330 million, which is still rising. Once cardiovascular disease occurs, it is generally progressive, which emphasises the importance of the prevention of cardiovascular disease. Paying attention to the screening of early organ damage of cardiovascular disease can carry out targeted cardiovascular risk stratification and classification, thus controlling the risk factors of cardiovascular disease and achieving early prevention.

Early cardiovascular organ damage includes the damage on large vessels, microvessels, heart, kidney, brain and the fundus. However, previous studies have mostly been done separately, and there is still a lack of corresponding reports on how to comprehensively and systematically evaluate early cardiovascular organ damage and explore prediction models and potential drugs to improve early cardiovascular organ damage and protect target organ function in patients.

Although the overall risk assessment and stratification system for cardiovascular disease is widely adopted by foreign guidelines, it is still difficult to consider the risk stratification system for cardiovascular disease, including the Framingham Heart Study (FHS),[2] the European Systematic Coronary Risk Estimation (SCORE) model,[3] the British QRISK score model,[4] the 2013 American College of Cardiology (ACC)/American Heart Association (AHA), and the Pooled Cohorts Equation (PCE) model for atherosclerotic cardiovascular disease (ASCVD) risk assessment developed by ACC/AHA.[5] All of the above models are the main cardiovascular disease risk assessment models established by European and American countries based on Western populations, which may be not applicable to the Chinese population. The China-PAR model established by Chinese scholars in 2016 for the assessment of 10-year risk and lifetime risk of cardiovascular disease was mainly based on the prediction for ASCVD risk in China.[6] However, this model pays less attention to early cardiovascular risk characteristics represented by early cardiovascular organ damage. Considering the high prevalence of cardiovascular disease in China, it is urgent to establish a good prospective cardiovascular disease cohort database based on the Chinese population, and to form a cardiovascular risk assessment system that combines the evaluation of early cardiovascular organ damage with the detection of risk factors of cardiovascular disease.

In 2013, our team conducted the Northern Shanghai Community Elderly Cardiovascular Patient Cohort Study (Northern Shanghai Study I), and the protocol of Northern Shanghai Study I has been published.[7] The study population was mainly located in Zhabei District, Putuo District and some other northern areas of Shanghai. Ten communities were randomly selected using a computer-generated list of communities. A total of 3590 participants were invited, of whom 3363 (93.7% response rate) agreed to participate in Northern Shanghai Study I. Northern Shanghai Study I was a risk assessment system designed to evaluate cardiovascular health in the elderly population, which included the cardiovascular risk factors, asymptomatic organ damage and cardiovascular diseases and carried out a 3-year follow-up, so as to keep track of organ damage situations, the main adverse cardiovascular events and deaths. After analysing the follow-up data, our team found a new indicator of early cardiovascular organ damage: arterial vascular age.[8] At the same time, some other research of our team has also revealed a new metabolic indicator of cardiovascular disease and key clinical indicators of early cardiovascular organ damage.[9–11] Based on these findings, we plan to conduct the Northern Shanghai Study II with an intent to achieve the following three research objectives: (1) establish the first Chinese-based database of all early cardiovascular organ structural and functional damage phenotypes, and establish a digital follow-up mechanism to create a prospective population-based cohort; (2) build a biobank (including blood, urine, faeces) for early cardiovascular organ damage in the Chinese population; and (3) explore a digital medication-based intervention and management system for early cardiovascular organ damage. This paper is to describe the design and method plan for this study.

METHOD

Study design

The Northern Shanghai Study II is a prospective ongoing study. This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board and was financially supported by the Science and Technology Commission of Shanghai Municipality (Grant No. 20dz1207200).

Sample size calculation

By querying data and referring to the queue of Northern Shanghai I, about 20.1% of the population in China had organ damage, and the prevalence of cardiovascular disease in China was estimated at 23.6%. Using these data as a reference, the sample size calculation was performed using the confidence intervals for one proportion. The formula is as follows:

$$n = \frac{Z^2_{\alpha/2}(1-P)P}{\delta^2},$$

where P is the overall rate, δ is the allowable absolute error, α=0.05, $Z_{\alpha/2}$ =1.96, target width=0.025. Considering the loss of lost samples during the follow-up process, the dropout rates were set to 10% for calculation. Take the maximum sample size from two proportions, and the estimated sample sizes were 4926. Considering the investigators' time and available resources, the final tentative minimum enrolment target is 4000–5000 cases.

Participant eligibility criteria

The inclusion criteria include: (1) aged between 18 and 75 years; (2) voluntarily participating in the study and having signed an informed consent; (3) able to accept long-term follow-up. The exclusion criteria are as follows: (1) diagnosed with severe heart disease (New York Heart Association(NYHA) IV) or end-stage renal disease (chronic kidney disease (CKD) ≥4); (2) be suffering from cancer or have a life expectancy <5 years; (3) had stroke within 3 months; and (4) refuse to participate in clinical research.

Recruitment

This research will recruit 4000–5000 Shanghai community residents. According to the inclusion and exclusion

criteria, we invite people between the ages of 18 and 75 to participate. The recruitment strategy comprises both online and offline methods. Specifically, it includes: (1) online recruitment: promotion through social media; (2) offline recruitment: posting research posters, such as research recruitment files in neighbourhood committees and community hospitals, and directly distributing recruitment leaflets to potential participants. Before data collection, the field staff will conduct a brief oral questionnaire based on the inclusion and exclusion criteria. When eligible individuals express interest in participating in the study, they will be fully informed and sign a consent form.

Comprehensive evaluation at the cardiovascular level

Northern Shanghai Study II emphasises patient-centred systematic evaluation and comprehensive management, and it will be conducted from cardiovascular risk factors and organ damage.The details are as follows:

Assessment of cardiovascular risk factors

Baseline data collection

The following baseline data, including gender, age, education level, lifestyle, smoking and drinking habits, diabetes history, renal insufficiency and cardiovascular diseases history, are collected by a standardised questionnaire and face-to-face interview. Cardiovascular diseases encompass chronic heart failure, peripheral vascular disease, hypertension, arrhythmia, and a history of myocardial infarction, stroke and/or cardiac revascularisation with either angioplasty or coronary artery bypass graft (CABG).

Physical examination

Anthropometric measurements

Height, weight, hip circumference, waist circumference, body mass index (BMI) and other anthropometric parameters of the participants are collected by the staff (see online supplemental appendix A).

Blood pressure

Office blood pressure and 24-hour ambulatory blood pressure are measured by professionally trained staff. All data are obtained from standard blood pressure measurements taken in the Shanghai Tenth People's Hospital. The instruments used are semi-automatic oscillometric devices (Omron Healthcare, Kyoto, Japan) and 24-hour ambulatory blood pressure monitors (Mobil-O-Graph NG, IEM, Germany) (see online supplemental appendix B).

Visceral fat monitoring

Visceral fat is measured using a HDS-2000 device (Omron, Japan). First, the shape of the abdomen (depth width/transverse width) is identified by the Omron DUALSCAN dedicated abdominal measuring instrument to obtain the total abdominal cross-sectional area. Then, the area of tissue (skeletal muscle/viscera) other than fat is measured based on the abdominal bioresistance (resistance value) generated by passing a weak current through the extremities. the area of subcutaneous fat is then measured on the basis of abdominal bioimpedance (resistance) generated by the passage of a weak current between the abdominal electrodes. Finally, the visceral fat area is obtained by subtracting the area of tissue other than fat and the area of subcutaneous fat from the total abdominal cross-sectional area previously obtained. The formula is as follows:

visceral fat area (cm^2)=total abdominal cross-sectional area–non-fat tissue area–abdominal subcutaneous fat area (see online supplemental appendix C).

Biochemical index examination

Blood lipid

Collect fasting venous blood from participants to conduct biochemical testing, primarily to measure the levels of lipids in the blood. These lipids include total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c). Standard methods are used to measure TC, HDL-c and TG,[12 13] and the Friedewald formula is applied to calculate the LDL-c.[14] Hyperlipidaemia is a major risk factor for cardiovascular disease and is a key indicator for metabolic assessment.[15 16] The optimal blood lipid levels for a population depend on the level of atherosclerosis cardiovascular disease risk stratification. Additionally, there are various coexisting diseases (such as hypertension, diabetes, CKD, stroke), special physiological conditions (pregnancy), elderly people and individuals with abnormal blood lipid metabolism, all of which require different normalisation levels of blood lipid management and treatment plans.[17] The specific data will be collected after the standard inspection by Shanghai Tenth People's Hospital is completed.

Blood glucose

The collection of fasting venous blood from participants is conducted for testing. The normal value of fasting plasma glucose (FPG) is in the range of 3.9–6.1 mmol/L. Diabetes can be diagnosed through elevated FPG, glycosylated haemoglobin (HbA1c) or abnormal oral glucose tolerance test. If symptoms are present, one abnormal test result is sufficient; if not, two abnormal test results are required.[18]

Blood, urine and stool routines

Under the supervision of experts, participants are obliged to gather the necessary blood, urine and faecal samples for testing. The main items of blood routine examination include red cell count, white cell count, platelet count, haemoglobin content and hematocrit, and the laboratory data can be used to preliminarily detect whether there is infection or blood system diseases. Urinalysis involves collecting fresh urine for analysis, and the main test items include pH, urine specific gravity, white blood cells, urine protein, urine glucose, urobilinogen and occult blood, which can help understand the body's metabolic status. Stool routine is to collect fresh stool to check for stool

Table 1 The severity of adult OSAHS depends on the severity of AHI and/or hypoxaemia

Degree	AHI (/hour)
Mild	5–15
Moderate	>15–30
Severe	>30
Degree	**The lowest Sao_2 (%)**
Mild	85–90
Moderate	80–<85
Severe	<80

white cells, red cells, parasite eggs, occult blood and other conditions, so as to understand whether the digestive tract has bacteria, virus and parasite infection. These three routines are used as routine examinations to obtain basic data of participants.

Homocysteine

Fasting overnight in order to obtain venous blood samples for testing, and all blood samples will be stored at −80°C. Under normal circumstances, the normal value of homocysteine in the human body is 5–15 µmol/L, and less than 6 µmol/L is the best state for the human body. Homocysteine is mainly derived from the daily diet and is an intermediate product of methionine and cysteine metabolism in the diet. Studies[19 20] have revealed that hyperhomocysteinemia can cause irreversible damage to the structure of arteries and trigger atherosclerosis, having a direct correlation with cardiovascular diseases.

Polysomnography

The apnea-hypopnea index (AHI), hypopnea index (HI), snoring and oxygen desaturation index (ODI) are collected by portable sleep apnoea monitor during sleep at home, and the paper report is given according to the diagnostic criteria of obstructive sleep apnea-hypopnea syndrome (OSAHS). The diagnostic criteria are shown in table 1.[21]

Assessment of organ damage

Cardiac damage

Electrocardiogram (ECG)

ECG is performed by an experienced cardiovascular specialist at the Shanghai Tenth People's Hospital, and all data are obtained from standard ECG reports at the Shanghai Tenth People's Hospital. One of the functions of ECG is to indicate abnormalities in cardiac structure. For example, if the Sokolow Lyon voltage on the ECG is >3.8 mV or the Cornell product is >244 mV·ms, it indicates left ventricular hypertrophy.[22]

Echocardiography

The measurements are performed by an experienced cardiovascular expert from the Shanghai Tenth People's Hospital. Atrial and ventricular parameters are measured according to the latest American Society of Echocardiography (ASE) guidelines for adult transthoracic echocardiography.[23] All measurements are obtained from standard cardiac ultrasound reports at the Shanghai Tenth People's Hospital.

Measurement of Left Ventricular Mass Index (LVMI)

Echocardiography is employed to measure interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular ejection fraction (LVEF), left ventricular end diastolic volume (LVEDV) and left ventricular end systolic volume (LVESV). To ensure precise radial measurements of IVST, LVPWT and the left ventricular internal diameter (LVID), they must be documented in the parasternal long axis view of the left heart.

By continuously measuring three end-diastolic values of LVEDV, IVST and LVPWT, the average values can be obtained. Applying Deiereux's left ventricular mass (LVM) correction formula, LVM (g) is then calculated. Finally, LVMI (g/m^2) is determined by dividing the LVM by the body surface area (BSA). The formulas involved are as follows[23]:

$$LVM\ (g)=0.8\times1.04\times[(IVST+LVPWT+LVID)^3-LVID^3]+0.6$$

$$BSA\ (m^2)=([height\ (cm)\times weight\ (kg)]/3600)^{1/2}$$

$$LVMI\ (g/m^2)=LVM\ (g)/BSA\ (m^2)$$

Assessment of global LV function

The left ventricular ejection fraction (LVEF) is a measure of the proportion of blood pumped from the left ventricle to the left ventricular end-diastolic volume per cardiac cycle. It is calculated using the double tip Simpson method,[24] which involves delineating the endocardial boundaries on the apical four chamber and apical two chamber sections and measuring the length of the cardiac cavity (L). The computer then uses standard calculation formulas to determine the left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV), and calculates the EF value. The formula is as follows:

$$LVEF\ (\%)=[(EDV-ESV)/EDV]\times100\%.$$

The myocardial performance index (MPI) or Tei Index can be measured by obtaining the isovolumic contraction time (IVCT), isovolumic relaxation time (IVRT) and the ejection time (ET) through pulse Doppler or tissue Doppler. This index is then calculated by using the formula:

$$MPI=(IVCT+IVRT)/ET.$$

Global longitudinal strain (GLS) is assessed through tissue Doppler imaging, with the longitudinal strain being obtained in four-chamber view, two-chamber view and three-chamber view, and the average strain value being calculated in the end. The GLS is reflective of the alteration in the long axis of the left ventricular endocardium between end-diastolic and end-systolic states. The formula is shown below:

GLS (%)=(end-systolic myocardial length–end-diastolic myocardial length)/end-diastolic myocardial length × 100%.

Measurement of cardiac diastolic function

Mitral diastolic flow velocity (E peak, a peak, E/A ratio)

Using colour Doppler flow in the four-chamber cardiac section of the apex, the pulse Doppler sampling volume obtains the peak velocity of early diastolic E peak (after ECG T wave) and late diastolic A peak (after ECG P wave) at the mitral apical level, and, subsequently, calculates the ratio E/A of the two.

E′ velocity and mean E/e′ of mitral annulus (lateral E′, septal E′)

The apical four-chamber view is taken and the tissue Doppler sampling volume is set to a range of 5–10 mm. The early diastolic maximum e′ (lateral e′ and septal e′) is measured at the lateral wall of the mitral annulus and the ventricular septum, with the average e′ being calculated. Subsequently, the E/e′ value is obtained by dividing the E peak velocity by the average e'.

Left atrial maximum volume index (LAVI)

Obtain apical four-chamber and two-chamber sections, freeze 1–2 frames prior to the opening of the mitral valve, maintain the maximum length and transverse diameter, measure the left atrial volume using two-dimensional ultrasound, and adjust the results with the body surface area.

Tricuspid regurgitation peak velocity (TRVmax)

To ascertain the maximum systolic velocity, continuous wave Doppler should be employed under colour Doppler flow mode to acquire the tricuspid regurgitation spectrum from the parasternal short axis and apical four-chamber view.

Myocardial injury biomarkers

Extract 2–3 mL of venous blood from participants for blood biochemical testing. The main biochemical markers of myocardial ischaemic injury detected include myocardial proteins and enzymes. The former includes high-sensitive cardiac troponin (hs-cTn), while the latter includes serum aspartate aminotransferase (AST), serum lactate dehydrogenase (LD) and its isoenzymes, serum creatine kinase (CK) and its isoenzymes, etc. The laboratory department of Shanghai Tenth People's Hospital will issue a comprehensive marker report, which is of great significance in ascertaining the time and intensity of myocardial injury and correctly classifying myocardial injury.

Renal damage

Participants will collect a morning urine sample, which will be kept at −80°C. Early damage of kidneys is estimated with ACR and estimated glomerular filtration rate (eGFR). ACR refers to the ratio of urine microalbumin to urine creatinine, which mainly reflects the reabsorption function of the renal tubules, and monitors whether there is early renal organ damage.[25]

Table 2 Assessment of the degree of carotid stenosis

Degree of carotid stenosis	PSV (cm/s)	EDV (cm/s)	PSV_{ICA}/PSV_{CCA}
Normal or <50%	<125	<40	<2.0
50%~69%	>125, <230	>40, <100	>2.0, <4.0
70%~99%	>230	>100	>4.0
Occlusion	No blood flow signal	No blood flow signal	No blood flow signal

CCA, common carotid artery; EDV, end-diastolic velocity; ICA, internal carotid artery; PSV, peak systolic velocity.

Vascular damage

Carotid ultrasound

Measurements are performed by an experienced cardiovascular expert from the Shanghai Tenth People's Hospital. All measurements are obtained from standard ultrasound reports of the Shanghai Tenth People's Hospital.

Carotid stenosis assessment

The peak systolic velocity (PSV), end-diastolic velocity (EDV) and PSV of the common carotid artery are collected using a 7.5 MHz sensor on both sides of the common carotid artery. Then the internal/common carotid PSV ratio is calculated. The degree of carotid artery stenosis is evaluated by table 2.[26]

Intima-media thickness

Carotid artery intima-media thickness (IMT) is determined by measuring the vertical distance between the anterior edge of the carotid artery lumen and the anterior edge of the media-adventitia surface. This measurement is taken 2 cm from the cardiac end of the left common carotid artery bifurcation. If a plaque is present in this area, the proximal segment of the plaque is used for the measurement; otherwise, the IMT of the vascular segment should not be taken. The thickest IMT and its location are recorded at the bifurcation of the common carotid artery and carotid artery.[27]

Carotid plaque

All longitudinal and transverse sections of the internal and external carotid arteries are scanned to determine the presence of plaques. The number of present plaques, plaque segments, and plaque properties (hyperecho/hypoecho/isoecho; homogeneity/inhomogeneity; morphological regular/irregular) are observed and recorded. The maximum plaque length and thickness are measured.

Carotid plaque is defined as an increment of IMT >50% of the surrounding wall thickness or IMT >1.5 mm on at least one side of carotid arteries.[27]

Ankle-Brachial Index (ABI)

Four-limb blood pressures are measured by professionally trained staff using a VP-1000 (Omron, Japan). Inter-arm and inter-leg systolic blood pressure (SBP) differences

are then calculated. The bilateral ABI defines as the ratio of ankle SBP divided by the brachial artery SBP, which is automatically measured and provided by the instrument.

Pulse wave velocity (PWV)

Brachial-ankle pulse wave velocity (BA-PWV) can be automatically obtained through the VP-1000 (Omron, Japan). For the measurement of carotid-femoral pulse wave velocity (CF-PWV), the SphygomoCor equipment (AtCor, Australia) is used. The participant is placed in the supine position, and the site of the most obvious pulse of the two target arteries is determined. The body surface distance between the two points is measured, and the pulse wave conduction time and pulse wave velocity are recorded. The SphygomoCor device provides a quality index and accepts only CF-PWV with a quality index greater than 80.

CF-PWV is the gold standard for detecting and assessing arterial stiffness (class I; Level of Evidence A),[28 29] and BA-PWV has been clinically examined with a strong association to cardiovascular disease risk factors. The degree of correlation between the two is comparable, making it a reliable indicator for evaluating cardiovascular disease.[30 31]

Organ damage of fundus

The assessment will be completed by fundus photography. This examination is performed by trained staff through colour fundus photography to provide a standardised fundus diagnosis report, including KW classification, arteriovenous ratio and the presence or absence of fundus arteriosclerosis/haemorrhage.

Definition of organ damage

In general, early organ damage consists of cardiac, vascular and renal organ damage. Left ventricular hypertrophy (LVH) is defined as LVMI ≥115 g/m^2 (male) or LVMI ≥95 g/m^2 (female),[32] and left ventricular diastolic dysfunction (LVDD) is assessed by E/E_a ≥15 or 8<E/E_a<15 with any of the following: LVMI >149 g/m^2 (male) or LVMI ≥122 g/m^2 (female).[33] Vascular damage include the presence of carotid plaque, increased carotid intima-media thickness (CIMT >900 µm), arterial stiffness (AS, CF-PWV ≥12 m/s) and peripheral artery disease (PAD, ABI <0.9)[34]; while chronic kidney diseases (CKD, eGFR <60 ml/min/1.73 m^2) and microalbuminuria (MAU, UACR >30 mg/mmol) represent renal damage.

Study outcomes and follow-up

The primary endpoint of this study is the composite of major adverse cardiovascular events (MACEs), including cardiovascular death, non-fatal stroke, non-fatal myocardial infarction or revascularisation ((percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG)). Non-fatal stroke is defined as the emergence of neurological symptoms or signs that last for at least 24 hours, with diagnosis supported by cranial CT or MRI. Non-fatal myocardial infarction is characterised by typical chest pain symptoms and/or characteristic ECG changes with troponin I >1.0 ng/mL or troponin T >0.1 ng/mL. Coronary artery revascularisation surgery, PCI or CABG, is defined as prior stent implantation (PCI) or CABG. Death diagnosis is based on a death certificate provided by a hospital or relevant department. Data collection for endpoint outcomes includes questionnaires, outpatient records and hospitalisation records, collected by personnel who are unaware of the statistical results.

Secondary endpoints of the study include: (1) newly diagnosed cardiovascular early organ damage such as left ventricular hypertrophy, reduced left ventricular diastolic function, augmented carotid IMT, arteriosclerosis, renal dysfunction (CKD 3 period) or increased microalbuminuria; (2) newly diagnosed cardiovascular or cerebrovascular diseases (including newly diagnosed hypertension, transient ischaemic attack, etc), or newly diagnosed renal insufficiency with proteinuria, or newly diagnosed diabetes.

Follow-up on cardiovascular events, deaths and organ damage every 2 years, expected to last for a total of 10 years. Specific details can be found in table 3.

Statistical analytic plan

Data collection and statistical analysis are conducted using SAS V.9.3. A Cox regression risk model is used for survival curve analysis, while a log-rank analysis is employed to compare differences between groups. Additionally, an ROC curve is employed to evaluate the impact of a certain risk factor on MACE events, with $p<0.05$ being defined as statistically significant.

Randomly selecting individuals for the exploration and validation set, scores will be generated on the exploration set and tested on the validation set. In order to identify important risk factors for cardiovascular events (CVEs), univariate analysis is conducted to evaluate the significance of various parameters. Traditional risk factors such as age, gender, smoking, obesity, diabetes, hypertension, blood sugar and blood lipids are considered, as well as organ damage risk factors including left ventricular hypertrophy, arteriosclerosis, vascular endothelial dysfunction, CIMT thickening, lower limb atherosclerosis, microalbuminuria and decreased renal function. Multiple logistic regression (MLR) is used to calculate the CVE risk factors β and compare the coefficients of organ damage and traditional risk factors. Variables with a significance greater than 5% will be added to MLR for stepwise regression. The regression coefficients of each independent variable in the Cox regression are then modified to construct a prognostic scoring model score (ie, exp(β)=HR). The ROC curve and area under curve are used to evaluate high-risk CVE populations, and sensitivity and specificity will be calculated for each cut-off score. The cut-off score with the highest score, the Youden Index, will be considered the optimal.

Data entry and management of data files

Data are entered into a computerised database through SAS software, V.9.3 (SAS Institute). To ensure accuracy,

Table 3 Baseline visit and patient follow-up

	Timepoints					
Measure	**Baseline**	**Every 2 years**	**Every 4 years**	**Every 6 years**	**Every 8 years**	**Every 10 years**
Consent form	✓	✓	✓	✓	✓	✓
Baseline questionnaire (age, gender, smoking and drinking habits, medication history, symptoms, diabetes history, renal insufficiency and CV diseases history, etc)	✓		✓			✓
Follow-up questionnaire (newly diagnosed cardiovascular or cerebrovascular events or kidney diseases or DM, etc)		✓	✓	✓	✓	✓
Physical data (height, weight, hip circumference, waist circumference, BMI)	✓		✓			✓
Office blood pressure measurement (three times in a row)	✓	✓	✓	✓	✓	✓
24-hour ambulatory blood pressure measurement	✓		✓			✓
Visceral fat monitoring	✓		✓			✓
Sleep assessment	✓		✓			✓
Venous blood biochemical parameters (blood glucose, blood lipid, serum creatinine, homocysteine, blood, urine and stool routine)	✓	✓	✓	✓	✓	✓
Cardiac organ damage (LVH: ECG: SV1+RV5; Echo: LVMI; LVDD: LVEF, GLS, MPI, E/A, E peak, A peak, lateral e′, septal e′, LAVI, TRVmax)	✓	✓	✓	✓	✓	✓
Renal organ damage (eGFR, creatinine, urinary microalbumin, serum urea)	✓	✓	✓	✓	✓	✓
Organ damage of four-limb and large artery vascular (limb blood pressure, ABI, carotid artery ultrasound, PWV)	✓	✓	✓	✓	✓	✓
Organ damage of fundus	✓	✓	✓	✓	✓	✓
Evaluation of peripheral artery involvement		✓	✓	✓	✓	✓
Major adverse cardiovascular events		✓	✓	✓	✓	✓
Cardiovascular deaths		✓	✓	✓	✓	✓
All-cause deaths		✓	✓	✓	✓	✓

ABI, Ankle-Brachial Index; BMI, body mass index; LVDD, left ventricular diastolic dysfunction; LVEF, left ventricular ejection fraction; MPI, Myocardial Performance Index; PWV, pulse wave velocity.

values that exceed the range or represent incorrect logic errors are double checked.

Patient and public involvement

Patient and public representatives were present on the ethics committee reviewing the design and research. The results of the study will be made available to participants on request.

Ethics and dissemination

This study was approved by the Shanghai Tenth People's Hospital Institutional Review Board. We plan to publish the results of this study in peer-reviewed journal articles. The results of the study will be shared through presentations at both national and international conferences.

DISCUSSION

Cardiovascular disease is the leading cause of death and disease burden in China, and it has also become a heavy health burden for families and society. According to the China Cardiovascular Health and Disease Report,[1] among the main causes of death for urban and rural residents, the constituent ratios of cardiovascular diseases were 44.26% and 46.74%, respectively, while the constituent ratios of malignant tumours were 25.73% and 23.27%. That is, the number of cardiovascular deaths in Chinese residents is about twice than that of cancer deaths. Both cardiovascular disease and cancer have three stages of development: pre-lesion, early lesion and end-stage lesion. They also share similar risk factors, such as genetics, advanced age, smoking, obesity, hypertension and diabetes. The 5-year survival rate of malignant tumours is 40%, and the 5-year survival rate of cardiovascular diseases such as heart failure is only 50%. At present, a series of preventive pre-cancer screening programmes have been established for tumours, such as genetic testing, biochemical testing, gastrointestinal endoscopy and surgical removal of polyps. It is urgent to establish a 'pre-cancer screening' system for cardiovascular diseases.

Asymptomatic early organ damage is the early stage of cardiovascular disease, which is similar to pre-cancerous lesions of tumours. Early assessment and intervention at this stage is a new direction in the field of cardiovascular prevention. In regard to cardiovascular prevention, this stage can be labelled as '1.5 level prevention'. Primary prevention of cardiovascular diseases involves taking steps to reduce risk factors before the onset of pre-existing cardiovascular diseases, such as unhealthy diet, prolonged sitting and inactivity, smoking and alcohol abuse, and irregular sleep patterns. Secondary prevention involves providing clinical treatment for patients who have already developed cardiovascular diseases, such as coronary heart disease, and taking timely medication for intervention. In between these two levels of prevention lies the concept of '1.5 level prevention'. Research has indicated that[35] the high incidence of clinical adverse outcomes in patients with cardiovascular diseases is often linked to early asymptomatic organ dysfunction. Therefore, early intervention in subclinical organ damage may help to prevent and reverse the occurrence of cardiovascular diseases. However, it is difficult to detect early organ damage in the cardiovascular system without conducting a comprehensive examination of early organ damage from the heart to the fundus, kidneys and large blood vessels.

In the future, a cardiovascular risk assessment and prediction model based on early organ damage will be conducted, and it is anticipated to implement the model in clinical practice to guide clinical decisions. In other words, except for the canonical evaluation of lifestyle health such as exercise habits, BMI, smoking and drinking habits, scores for early organ damage can also be obtained, which will enable us to gain an insight of patients' cardiovascular health status and create tailored treatment plans. Consequently, through offering early prevention and treatment measures, we can reduce the risk of cardiovascular disease, minimise the potential for negative medical outcomes, and ultimately, improve patients' life quality.

In addition to the prediction model, a biobank for early cardiovascular organ damage in Chinese population, including blood, urine, faeces, and all data will be uniformly stored, managed, updated by a dedicated person authorised by the researchers, and automatically generated into a unified digital report. This digital report may continue to be used in future intervention studies.

To further our research, we will conduct clinical trials to assess the efficacy of targeted interventions, such as medication, in reversing cardiovascular damage and improving outcomes. For instance, the PACMAN AMI study,[36] a randomised, double-blind clinical trial involving 300 patients with myocardial infarction, found that the use of PCSK9 inhibitors in combination with high-intensity statins can reduce LDL-c levels, stabilise high-risk plaques, and even cause plaque reversal, providing clinical benefits.

Ideally, we would investigate the effect of early organ damage on terminal events among participants who are free of all cardiovascular diseases. Nevertheless, we acknowledge that milder cardiovascular diseases (eg, NYHA ≤III) may also be affected by early organ damage, and this population is relatively large. Therefore, we have decided to include this group of people in our study, excluding only those with severe cardiovascular diseases (eg, NYHA IV).

In summary, we intend to create a prospective cohort based on a Chinese population, with a focus on the standardised and traceable assessment of early cardiovascular organ damage.

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Appendix A

Specific measurement methods for height, weight and other dimensions

1. Participants are asked to stand with their shoes off during height measurement. Height is defined as the distance (cm) from the sole of the feet to the highest point of the skull.
2. Body weight (kg) is measured by standing on a body weight scale wearing light clothes and shoes off.
3. To measure the hip circumference, the participant should stand upright with their feet together and their arms naturally hanging down, and the tape should be measured around the level of the fullest buttocks for one week. The tightness of the tape should be suitable for easy rotation.
4. To measure waist circumference, participants should stand straight with their feet together, their arms should drop naturally, their abdomen should not be retracted, their breathing should be steady, and the tape measure should be placed around the narrowest part of the waist (the narrowest part above the hip bone and under the ribs) for one week, and waist circumference (cm) should be observed and recorded.
5. Calculate body mass index (BMI), which is defined as the weight divided by the square of the height (kg/m^2).

Appendix B

Specific measures of blood pressure

1. Office BP measurement

After an overnight fast, participants are instructed to empty their bladder before blood pressure measurement, not exercise vigorously for approximately 30 minutes before blood pressure measurement, not smoke cigarettes, or drink caffeinated beverages (e.g., tea, coffee, or cola). Participants are seated in a comfortable position, with their hands and elbows resting flat on the table and their feet resting naturally on the floor. Bare upper arms, heavy coat should be removed, do not roll up the sleeves. The upper arm should be at an angle of about 40°to the chest wall, at the same level as the heart.

Participants rest in a seated position for at least five minutes to relax and avoid anxiety and agitation.They are then instructed to wrap the cuff from above with their palms up. The bottom of the cuff should be located one to two centimeters above the medial elbow of the upper arm, about two transverse fingers, the cuff should be tight and suitable, not covering the elbow joint, and the air tube should be on the extension line of the middle finger. Blood pressure is then measured with the use of a semiautomatic oscillometric device (Omron Healthcare, Kyoto, Japan), and two or three measurements are taken at the same site, with an interval of two to three minutes, and the two differences of less than 5 mmHg are recorded, averaged, and recorded.

2. 24-hour ambulatory blood pressure measurement

First, the arm circumference should be measured, and the appropriate sphygmograph cuff should be selected according to the size of the arm circumference. As with office BP measurement, most adults typically choose a standard cuff; patients with obesity and a large arm circumference (≥ 32 cm) should choose a large cuff. On the other hand, if the upper arm circumference is small (< 24 cm), a small cuff should be selected.

Before ambulatory blood pressure monitoring, the office blood pressures of both arms are measured, and the results of previous bilateral blood pressure measurements are known. If the difference in blood pressure between the two arms is ≥ 10 mmHg, the upper arm with higher blood pressure should be selected for ambulatory blood pressure monitoring. If the difference of office blood pressure between the two arms is ＜10 mmHg, the non-dominant arm is selected for ambulatory blood pressure monitoring to reduce the influence of arm movement on blood pressure monitoring.

A 24-hour ambulatory sphygmomanometer (Mobil-O-Graph NG, Germany) is used to test whether the sphygmomanometer is working properly by manually measuring it twice after wearing it. At baseline, blood pressure is measured every 30 minutes, with a difference of 5 mmHg or less between 24-hour ambulatory blood pressure measurements and office measurements. Data from the first hour are excluded from the analysis, and data from the next 24 hours are used. Participants are asked to record the time of daily activities (bedtime/wake up, sleep status, meals, bowel movements, and medication). Stop if pain or numbness occurs in the upper arm while the cuff is inflated. Patients are advised not to drive or operate any other dangerous machinery or work at altitude.

Appendix C

Specific measurement procedures for visceral fat detection

1. The patient's information is input into the host of the device, and the patient is placed in the supine position and rested for 1 to 2 minutes before the test.
2. Let the patient wear the abdominal measuring device, align the measuring end at the center of the navel, guide the patient to gently breathe and hold his or her breath, and press the OK button of the measuring device.
3. Install the simple pad on the electrode belt and wear it on the abdomen, wear the electrode clip for hand and foot, guide the patient to breathe lightly and press the start button. The measurement time is about 5s, and print the examination result report after the measurement.