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Northern Shanghai Study: cardiovascular risk and its associated factors in the Chinese elderly—a study protocol of a prospective study design

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ABSTRACT

Introduction: Cardiovascular (CV) diseases are the leading cause of death and disability in the world. Increasing lifespans and ageing populations also contribute to an increasing CV burden. However, in China, there were few well-designed cohort studies focusing on the elderly population, let alone an established CV risk score. The objective of this study is to establish a CV risk score based on a community-dwelling Chinese elderly population, determining the profile of the associated CV 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 enrolment, clinical examination, anthropometric measurement and a questionnaire will be administered to 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, 4-limb blood pressure recording, body mass index, etc. Baseline measurement will also include the assessments on TODs and the conventional CV risk factors. In the follow-up, the incidence of CV events and mortality will be recorded. The Northern Shanghai Risk Score will be calculated, with considerations 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.

Trial registration number: NCT02368938; Pre-results.

Strengths and limitations of this study

- This study is one of the largest ongoing prospective population studies to evaluate target organ damages (TODs) in the community-dwelling elderly Chinese, which is authorised and funded by the Shanghai municipal government.
- A systematic framework of a cardiovascular (CV) risk survey was conducted, with considerations on conventional CV risk factors, asymptomatic TODs, CV diseases, future events and mortality.
- Left ventricular ejection fraction was measured by the M-mode echocardiograph, but not by Simpson's method.
- The risk score is based on the elderly participants, who are 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.
- Some measurements in this study need highly specialised equipment, which is hard to scale to a larger population.

BACKGROUND

Cardiovascular diseases (CVDs), as ageing-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 reduction in a 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 CV risk score in China.

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

The current risk scores in the USA and Europe are based on a mainly Caucasian general population. However, in China, things would be different. According to the *World Population Ageing 2013*, it will take China only 26 years to experience the population ageing, which means there is a rapid ageing trend in China. On the other hand, China also had the most rapid urbanisation 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 urbanised 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 urbanisation 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 CV 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 CV 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 CV risk score based on a 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) in the northern Shanghai area. The assessments include conventional CV risk factors, TODs 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 financial support from the Shanghai municipal government (grant ID: 2013ZYJB0902 and 15GWZK1002). The preliminary sample size is expected to be 3000–4000 participants.

Participant eligibility criteria

The inclusion criteria include: (1) age 65 years or more; (2) informed consent should be signed voluntarily; (3) local residents from communities in northern Shanghai and (4) available for long-term follow-up. The individual 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 <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 or (7) loses contact with the laboratory staff.

Recruitment

First, according to the *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 enrolment. Other communities in the list will be randomly selected for the later enrolment. According to the inclusion and exclusion criteria, we invite all the eligible older people (over 65 years) to participate in this study.

The recruitment strategies include: (1) posting study recruitment files in the neighbourhood committees and community hospitals; (2) according to the health file, community hospitals recruit the potential participants

by telephone; (3) hand out recruitment flyers directly to the potential participants. Contact number is included in all the recruitment files and flyers. Before data collection, the field staff will give a brief oral questionnaire according to the inclusion and exclusion criteria. When the eligible individual shows their interest 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 standardised 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 CV event (the presence of a history of myocardial infarction (MI) and/or stroke and/or cardiac revascularisation with either angioplasty or coronary artery bypass graft (CABG)).

Participants 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 a flexible rule, with waistline and hipline referring to the smallest waist and the greatest circumferences, respectively. The body mass index is calculated by dividing body weight (kg) by the squared body height (m^2).

Venous blood samples are obtained after an overnight fast. Total cholesterol, high-density lipoprotein cholesterol and triglycerides are measured by standard methods,[18 19] and the 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 recorder's name will be recorded.

Office blood pressure measurement

After an overnight fast, brachial blood pressure is measured in the morning with the participants' bladder empty, free of tobacco or caffeine for at least 30 min before the measurement. The blood pressure is measured in the sitting position, after resting for 5 min, using a semiautomatic oscillometric device (Omron Healthcare, 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 measurements are performed with a 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 (LV) internal diameter at end-diastole (LVIDd) and septal (SWTd) and posterior wall thickness at end-diastole (PWTd) are measured directly. The formula:

$$LVM\,(g) = 0.8 \times [1.04 \times [(LVIDd + PWTd + SWTd)^3 - (LVIDd)^3]] + 0.6$$

is used to calculated the LV mass, based on modelling the LV as a prolate ellipse of revolution.[22] The left ventricular ejection fraction (LVEF) is calculated by Teichholz's formula, and the left atrium (LA) size is measured in the parasternal long axis and apical four-chamber views. Left atrial volume is calculated using the ellipse model formula:

$$\text{left atrial volume} = \pi \times (SA1 \times SA2 \times LA) / 6$$

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 (IMT) 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. The plaque is defined as IMT of the internal carotid artery of more than 1.5 mm[24] or a localised echo-structure encroaching into the vessel lumen with the arterial wall above 50% thicker than neighbouring 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 Healthcare, Kyoto, Japan) automatically, performed by 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 subsequent studies.

Pulse wave velocity

Pulse wave velocity (PWV), which can be estimated by the SphygomoCor device (AtCor, Australia), is measured in a defined segment to assess the arterial stiffness.[25] It

is recommended that the arterial stiffness should be determined non-invasively 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]

Participants need to rest quietly in a temperature-controlled room for at least 10 min 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 >80% is considered as a reliable measurement, in which the quality and reproducibility of the tonometry measurements are automatically tested.

Pulse wave analysis

Pulse wave analysis, which can be observed on the commonly used device—SphygomoCor device (AtCor, Australia),[30] is measured to estimate central haemodynamic parameters.[31] SphygmoCor is used to perform the applanation tonometry on a radial artery with the methodology previously described.[30] After a 10 min rest in the supine position, the brachial BP is obtained with the SphygomoCor device. Then a radial waveform is recorded by one trained and experienced physician with a tonometry-based probe. The central waveform is estimated by the inbuilt software, automatically, with the help of a validated generalised 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 are 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 standardisation with standard equipment after at least a 5 min rest. 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 LV hypertrophy are as follows: Sokolow-Lyon-Rappaport index (SV1 or SV2+RV5 or RV6≥4.0 mv in men and SV1 or SV2+RV5 or RV6≥3.5mv in women), Cornell criterion (SV3+RaVL≥2.8mv in men and SV3+RaVL ≥2.8 mv in women) and Cornell Product ((SV3+RaVL)×QRS duration≥244mv·ms in men and (SV3+RaVL+0.6)×QRS duration≥244 mv·ms in women).

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 inbuilt software using a 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.

LV hypertrophy is defined as LVMI ≥115 g/m^2 (men) or LVMI ≥95 g/m^2 (women).[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/1.73 m^2) and microalbuminuria (UACR >30 mg/mmol) represent renal TODs. Specifically, LV diastolic dysfunction is present when ≥3 listed variables meet these cut-off values (septal e′, 7 cm/s, lateral e′, 10 cm/s, average E/e′ ratio, 14, LA volume index, 34 mL/m^2).[34]

Clinical outcome

The primary outcome is a composite of major adverse cardiovascular events (MACE), including CV death, non-fatal stroke, non-fatal MI or revascularisation (percutaneous coronary intervention (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 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 revascularisation with either PCI or CABG is defined as a history of either stent implantation (PCI) or CABG. A death diagnosis is identified on the basis of a death certificate given by the related hospital. The end point is defined by a combination of a questionnaire, dropping-in follow-up and review of the computerised medical records of clinic visits and hospitalisations, conducted by a blinded end point evaluating committee.

The secondary outcome includes: (1) subclinical organ damage which is defined as LV hypertrophy or decreased diastolic function or increased carotid IMT and/or the presence of plaque or hardening of the arteries or renal insufficiency (CKD3 period) or increased microalbuminuria; (2) newly diagnosed CV or cerebrovascular disease (including newly diagnosed hypertension, transient ischaemic attack, etc), or newly diagnosed renal insufficiency with proteinuria or newly diagnosed diabetes mellitus (table 1).

Table 1 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 (including newly diagnosed cardiovascular or cerebrovascular events, kidney disease and 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 microalbumin 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 proportional hazards regression model and survival among groups will be compared using the log-rank test. The 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, V.9.3 (SAS Institute, Cary, North Carolina, 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 a predictable value for cardiovascular events (CVE) are LV hypertrophy, arterial stiffening, carotid hypertrophy, lower limb atherosclerosis, microalbuminuria and renal function decline.[35] The conventional risk factors for CVE include age, gender, smoking, obesity, diabetes, hypertension, blood glucose and lipid profile. The independent variables are defined and categorised as follows: LV hypertrophy: LV mass index >115 g/m^2 for men and >95 g/m^2 for women; arterial stiffening: cf-PWV>12 m/s; carotid hypertrophy: IMT ≥0.9 mm; lower limb atherosclerosis: ABI ≤0.9; microalbuminuria: UACR >30 mg/mmol; renal function decline: stage 2 CKD: eGFR 60–89 mL/min/1.73 m^2 (MDRD); stage 3 or more CKD: eGFR <60 mL/min/1.73 m^2 (MDRD); age is categorised 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 (ie, exp (β)=HR).[37] A p value of ≤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. An 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

Since 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 will be used to measure 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 cut-off 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 computerised database with SAS software, V.9.3 (SAS Institute, Cary, North Carolina, USA). Values that are out of range or represent errors of faulty logic are avoided by double check.

DISCUSSION

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

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

Some well-established CV risk scores from famous population studies were widely adopted, 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 microdamages from conventional risk factors have been converted into 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. For this patient, the CV risk from long-term exposure to smoking has turned into severe atherosclerosis. The intervention of smoking cessation would be less beneficial compared with the lipid-lowering therapy. For the Chinese elderly, some TODs 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 ageing population.

In summary, 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 a chance to provide the Chinese policymakers 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 of those 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 TODs with conventional CV risks. We will analyse the change of the TOD indicators at every 2–5 years, and we will conduct new enrolment at the same 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 future CV events, providing a 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.

Contributors HJ, JX, SY, CC, XF, BB, YZho, JT, YL and YZha acquired the original data for this study. YZha and YX formulated the methods and designed the protocol. HJ and JX drafted the manuscript. HX helped us with the writing and language review. All authors contributed to revisions and approved the final version of the manuscript.

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Competing interests None declared.

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