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Population-based Cohort Study in Outcome of Phased Progression of Atherosclerosis in China (PERSUADE): objective, rationale and design

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Abstract

The coronary artery calcification score and pericardial fat volume have recently been reported to be strongly associated with the severity and presence of coronary atherosclerosis. However, no studies have explored the outcome of phased progression of atherosclerosis by non-contrast computed tomography in asymptomatic people in China. The population-based cohort study in outcome of phased progression of atherosclerosis in China (PERSUADE), an observational, longitudinal and prospective cohort study in a target population of healthy subjects based in Jidong Oilfield (China), prospectively analyzes the outcome of phased progression of atherosclerosis by non-contrast computed tomography in healthy population. The results of this study are expected to be of value for utilizing noninvasive imaging combine with traditional cardiovascular risk factors to create a risk stratification and find pertinent biomarkers associated with the outcome of phased progression of atherosclerosis in healthy people, thereby could help to establish a more personalized treatment of clinical practice.

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Keywords: Atherosclerosis; Cardiovascular events; Chest computed tomography

1 Background

Atherosclerosis is the underlying cause of most cardiovascular diseases and the leading cause of death and disability world wide. Currently, it has been illustrated that atherosclerosis starts with fatty streaks formation and progresses with atherosclerotic plaque formation. Previous studies also demonstrated that hypercholesterolemia, hypertension, diabetes, and dysfunction of endothelium are the common facilitating factors for atherosclerosis.^[1,2] However, there are substantial differences in its incidence, prevalence and mortality across countries and ethnicities. Morbidity and mortality of cardiovascular disease have decreased significantly in developed countries, but continue to rise in developing

countries.^[3] The changes in lifestyle and diet have lead to an increase of life expectancy, but also of the burden of cardiovascular disease and other chronic diseases.^[4] Developing efficient preventive approaches for atherosclerosis progression may be an effective strategy to minimize the risk of cardiovascular events among general populations. Early detection may lead to optimum therapeutic intervention. Noninvasive measurement of the subclinical atherosclerotic burden in asymptomatic people has the potential to improve assessment of cardiovascular risk and might contribute to a more effective prevention of cardiovascular events.

Recently, the discovery that pericardial fat may locally affect coronary arterial through generation of inflammatory cytokines.^[5] Moreover, coronary artery calcification has been strongly recommended to be added as one of the risk factors for predicting adverse cardiovascular events.^[6] In terms of technology, non-contrast chest computed tomography (NCT) can be routinely performed to detect pericardial fat volume (PFV) and measure coronary artery calcification score (CACs).^[7,8] Given the high prevalence of atherosclerosis, studying risk factors or characteristics for

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atherosclerosis in Chinese population will have greater public health and clinical implications.

A growing body of evidence reveals that cardiac fat deposits maybe associated with multiple metabolic risk factors, such as hypertension, hyperlipidaemia and diabetes, with an unfavorable cardiometabolic risk profile suggesting that a high pericardial fat accumulation might play a major role in the pathogenesis of coronary atherosclerosis disease (CAD), and as a new biomarker for cardiovascular risk assessment.^[9] Previous researches have reported CACS had correlation with PFV, but no correlation with body mass index (BMI) and blood lipid levels. Therefore, PFV may have a unique role in coronary artery calcification even in atherosclerosis progression. Nakanishi R, *et al.* demonstrated that increase in epicardial fat volume is associated with greater CACS progression in subjects at intermediate risk by coronary calcification score.^[10] Contrary to the previous reports, Wassel, *et al.*^[11] studied the relationship between the PFV and the coronary calcium score in 600 patients using chest computed tomography (CT) scans at two time points with an interval of about four years, and found that PFV is not associated with the presence, severity and progression of coronary artery calcium. However, there is no comprehensive evaluation of the effects of CACS, PFV and cardiovascular events in China.

2 Objective

Our main aim is to spread the noninvasive imaging and proper biomarker associated with the outcome of phased progression of atherosclerosis in healthy people. Baseline examination consists of screening for CACS and measurement of PFV by non-contrast chest computed tomography, as well blood sampling for determination of traditional risk factors will be collected. Moreover, follow-up at annual year will include a repetition of baseline measurements and cardiovascular events.

3 Methods

3.1 Study design and population cohort

The PERSUADE study is an observational, longitudinal, prospective cohort study that will include 3000 asymptomatic participants of Jidong Oilfield community for a total of 10 years of follow-up (Figure 1). The community is geographically located in Tangshan City in northern China and is mainly comprised of employees of the Jidong Oilfield and their family members. From April 2014, all residents aged 40 to 75 years were invited to participate in our study at the

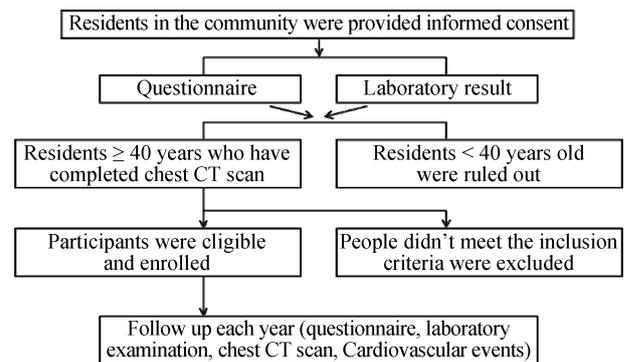


Figure 1. Flowchart of PERSUADE study.

time of their regular annual check up performed by the Jidong Staff Hospital.

The following are the exclusion criteria: (1) prior history of cardiovascular disease (including myocardial infarction, angina pectoris, stroke, peripheral vascular disease, aortic aneurysm, angioplasty, heart surgery, atrial fibrillation, heart failure, heart valvular diseases or any other heart disease); (2) active treatment for cancer, history of transplant with active immunosuppressive or immunomodulator treatment; (3) morbid obesity (body mass index ≥ 40 kg/m²), chronic kidney disease (glomerular filtration rate < 60 mL/min per square meter), presence of any disease that decreases life expectancy to < 5 years, or any condition that could affect adherence to the study procedures; (4) participants are also excluded if they were pregnant or lactating.

3.2 Data collection

All data is obtained at the annual medical exam that the Jidong Oilfield provides to all workers and their family. The clinical exam follows standardized protocols using validated procedures and instruments. Data collection at the annual medical exams is conducted by the physicians and nurses of the Jidong Staff Hospital, who undergo training and standardization programs organized by the study investigators. Basic demographic information of all participants is collected by trained doctors using validated questionnaire specifically designed for this study.

3.3 Assessment of demographic variables and cardiovascular risk factors

Detailed information on demographic variables (e.g. age, gender, household income, level of education, and previous history of diseases) are collected. The average monthly income is categorized as “ $< ¥ 3,000$ ”, “ $¥ 3,000-4,999$ ” and “ $\geq ¥ 5,000$ ”. The level of education is categorized as “illiteracy or compulsory education”, “high school” or “College/University”. The smoking status is classified as “never”, “former”, or “current” according to self-reported information.

Body weight (kg) and body height (cm) are measured, and the body mass index is calculated as body weight (kg) divided by the square of height (m²). Hypertension is defined based on the following information alone or in combination: (1) as presence of a history of arterial hypertension; (2) using antihypertensive medication; or (3) a systolic blood pressure > 140 mmHg or a diastolic blood pressure > 90 mmHg. Diabetes mellitus is defined as a self-reported history, current treatment with insulin, oral hypoglycemic agents or fasting blood glucose level > 126 mg/dL. Dyslipidemia is defined by a self-reported history, current use of cholesterol lowering medicine, a total cholesterol level > 220 mg/dL or triglyceride > 150 mg/dL or low density lipoprotein > 160 mg/dL.

3.4 Laboratory analysis

At each examination, blood samples are collected from the antecubital vein in the morning under fasting conditions. They will be stored in vacuum tubes containing Ethylene Diamine Tetraacetic Acid (EDTA). Fasting blood glucose will be measured with the hexokinase/glucose-6-phosphate dehydrogenase method. Cholesterol and triglyceride concentration will be measured enzymatically [inter-assay coefficient of variation: < 10% (Mind Bioengineering Co. Ltd, Shanghai, China)]. For all participants, serum creatinine, cholesterol, low-density lipoproteins (LDL-C), triglycerides as well as glucose levels will be assessed.

3.5 Analysis of CACS and PFV

As part of the protocol, all participants will undergo NCT for quantification of CACS and PFV. The NCT is acquired using a 64-slice CT scanner (Siemens Dual Source 64-Slice Definition, Forchheim, Germany). For scanning, a standard non-contrast prospective scan will be performed. Acquired images will be then transferred to a research workstation for quantification of CACS and PFV. All CT images will be initially reviewed by two experienced CT analysts using semiautomatic, commercially available software (synoMultiModality Workplace, syngoMMWP VW 40A).

CACS is defined as a focus of at least four contiguous pixels with a CT density of > 130 Hounsfield units (HU) and quantified using the Agatston method. Total Agatston CACS is calculated as the sum of calcified plaque scores of all coronary arteries. Pericardial fat includes all adipose tissue enclosed by the visceral pericardium, involving all fat directly surrounding the coronary arteries. Image data will be processed as following. First, the upper slice limit marked by bifurcation of the pulmonary trunk, and lower slice limit identified as the last slice containing any portion of the heart, are manually chosen by an expert reader

blinded to patient status and clinical NCT interpretation. Next, the reader defines five to seven control points on the pericardium in each transverse view. The PFV is then automatically calculated (reported in cm³). Contiguous 3-dimensional voxels between the HU limits of -195 to -45 are defined as fat voxels.

3.6 Follow up and outcome assessment

Participants will be followed up by face-to-face interviews every year in a routine medical examination. Data on clinical outcomes will be collected through a standard operational procedure follow up system. The follow up system involves linkage of the study database to files from general practitioners, medical specialists and discharge reports in case of hospitalization. With respect to the vital status of participants, the information is also obtained regularly from the municipal health authorities in Tangshan city. After notification, cause and circumstances of death will be diagnosed by general practitioners using questionnaire.

The disease diagnosis will be confirmed only after review of the medical records by an End Points Committee of physicians that includes a cardiologist, neurologist, cancer experts, etc. The End Points Committee of physicians including membership, role and responsibilities will be approved before the start of the study by the executive committee. Primary endpoints are major adverse cardiovascular events (MACE) including cardiac death, myocardial infarction, stroke and revascularization. In brief, questionnaires on the current state of health including questions about current medications, hospital admissions, and outpatient diagnosis of cardiovascular disease are annually sent to the participants. In parallel, all death certificates are regularly screened. Incident cardiovascular morbidity and fatal events will be validated by reviewing hospital records and records of the attending physicians, and classified by an external endpoint committee, blinded to the risk factor status and the CACS.

3.7 Statistical analyses

The data management system including the statistical analysis is performed using the SAS software (version 9.4; SAS Institute, Cary, North Carolina, USA). Firstly, the distributions (mean \pm SD) of the parameters are calculated. Normal distribution of the parameters is assessed using the Kolmogorov-Smirnov test. Secondly, the parameters are compared between the groups, using either the student's *t* test for paired or non-paired samples of normally distributed parameters or the Wilcoxon-Mann-Whitney test or the Wilcoxon test for non-parametric variables. The Chi-squared test is applied for the comparison of categorical variables. Thirdly, multivariate associations between the

various parameters are performed using multivariable regression analyses or binary regression analyses. Fourthly, a longitudinal assessment of associations and a survival analysis for the combination of major vascular events and for each vascular event will be performed using the Kaplan-Meier curves in relation to PFV. Cox multivariate regression models will be used to compare the probability of having a vascular event in the follow-up cohorts, adjusting for the possible confounders. The hazards ratios (HR) will be presented with their corresponding 95% confidence intervals (CI). The level for statistical significance will be set at $\alpha = 0.05$ (two-tailed).

3.8 Ethics statement

The study protocol is complied with the World Medical Association Declaration of Helsinki and China's regulations and guidelines on good clinical practice. Ethical clearance for the trial has obtained from the Ethical Committee of the Jidong Staff Hospital. Informed consents will be obtained from all participants before recruiting into the study.

4 Discussion

The PERSUADE study will prospectively evaluate the relation between non-invasive CT imaging based risk factors and phased progression of atherosclerosis in asymptomatic population in China. In a planned long-term follow up, data from clinical parameters, laboratory tests, CACS, PFV and the occurrence of cardiovascular events will be collected longitudinally to build up a predicting model for the risk of atherosclerosis progression.

Atherosclerosis is a long-term condition that progresses over many decades. It usually produces no symptoms until that arterial narrowing significantly reduces blood supply to an organ. So early intervention and preventive strategies have become major targets for predictive, preventive and personalized medical studies. Previous hospital-based studies have indicated relationship between traditional cardiovascular risk factors and atherosclerosis progression.^[12-16] For example, participants from the cohort of the Korean Atherosclerosis Study 2 ($n = 402$, mean age of 54 years, 57.0% men) underwent 64-slice multi-detector row computed tomography (MDCT) to assess pericardial fat amount, CACS, severity of coronary artery stenosis, and plaque characteristics. Patients with atherosclerotic lesion had significantly larger volume of pericardial fat than patients without atherosclerosis ($308 \pm 96 \text{ cm}^3$ vs. $251 \pm 93 \text{ cm}^3$; $P < 0.01$).^[7] Our study is a population based survey, and the participants underwent NCT for CACS and PFV measurement every year to evaluate the atherosclerosis risk factors.

In this study, we had focus on the CACS and PFV by NCT. NCT screening requires no preparation and avoids the use of intravenous contrast. This technique can be operated in any participants able to lay flat and perform a single breath hold. The participant is exposed to a low dose of radiation less than 1 mSv, akin to mammography and less than annual exposure from natural sources (3–4 mSv). To date, CACS has been applied to more than 100,000 participants, including multiple large prospective studies with up to 10-year follow up.^[17,18] Across these studies, CACS has demonstrated a consistent ability to assess cardiovascular risk in asymptomatic patients beyond that provided by alternative noninvasive tests and risk calculators. In a subset of participants in the cardiovascular health study, CACS and intima-media thickness (IMT) seemed to predict CVD events in a similar manner, but IMT outperformed CACS for stroke prediction.^[19]

It has been postulated that paracrine effects of pericardial fat may be a potent determinant of coronary plaque development and progression. Pericardial fat, owing to the anatomical proximity with coronary arteries and heart, has been found to contain higher levels of inflammatory markers and adipokines that can locally accelerate the atherosclerotic process by endothelial dysfunction, local proliferation of smooth muscle cells and increased plaque instability through apoptosis and neovascularization.^[20, 21] PFV increment has been observed to have a strong association with various inflammatory marker changes and early coronary endothelial dysfunction that may precede coronary calcification and the development of mature atherosclerotic changes.

The present study has several strengths, including its large sample size, the stability and low mobility may facilitate longtime follow up examinations. Moreover, our NCT is noninvasive examination and radiation dose is very low. Nevertheless, several limitations of this study should be considered. Firstly, this is a single-centre investigation, and the participants are in the northern of China, so it couldn't completely stand for whole Chinese population. Secondly, our measuring method for quantifying PFV is semi-automatic and we cannot accurately measure the epicardial fat volume by non-contrast methods. Thirdly, because of the non contrast, we can not obtain the condition of coronary artery stenosis.

In brief, the PERSUADE study is expected to analyze the clinical characteristics of asymptomatic people and to set up risk stratification model by collecting the cardiac CT imaging and risk factors. Combining with follow up of cardiovascular events, the present study may help to achieve early detection, early prevention of the cardiovascular disease and establish a more personalized treatment of clinical practice.

5 The study status

This program began in April 2014 and patients' follow up visit is ongoing now. The baseline clinical information was collection and exam data will be transfer and arrange into our database every year then.

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References

- 1 Asgary S, Solhpour A, Parkhideh S, *et al.* Effect of hydroalcoholic extract of *Hypericum perforatum* on selected traditional and novel biochemical factors of cardiovascular diseases and atherosclerotic lesions in hypercholesterolemic rabbits: A comparison between the extract and lovastatin. *J Pharm Bioallied Sci* 2012; 4: 212–218.
- 2 Tonelli M, Riella MC. Chronic kidney disease: chronic kidney disease and the ageing population. *Nat Rev Nephrol* 2014; 10: 127–128.
- 3 Beckman JA, Creager MA, Libby P, *et al.* Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA* 2002; 287: 2570–2581.
- 4 Wang L, Kong L, Wu F, *et al.* Preventing chronic diseases in China. *Lancet* 2005; 366: 1821–1824.
- 5 Soliman EZ, Ding J, Hsu FC, *et al.* Association between carotid intima-media thickness and pericardial fat in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Stroke Cerebrovasc Dis* 2010; 19: 58–65.
- 6 Wheeler GL, Shi R, Beck SR, *et al.* Pericardial and visceral adipose tissues measured volumetrically with computed tomography are highly associated in type 2 diabetic families. *Invest Radiol* 2005; 40: 97–101.
- 7 Kim TH, Yu SH, Choi SH, *et al.* Pericardial fat amount is an independent risk factor of coronary artery stenosis assessed by multidetector-row computed tomography: the Korean Atherosclerosis Study 2. *Obesity (Silver Spring)* 2011; 19: 1028–1034.
- 8 Tamarappoo B, Dey D, Shmilovich H, *et al.* Increased pericardial fat volume measured from noncontrast CT predicts myocardial ischemia by SPECT. *JACC Cardiovasc Imaging* 2010; 3: 1104–1112.
- 9 Rosito GA, Massaro JM, Hoffmann U, *et al.* Pericardial fat, visceral abdominal fat, cardiovascular disease risk factors, and vascular calcification in a community-based sample: the Framingham Heart Study. *Circulation* 2008; 117: 605–613.
- 10 Nakanishi R, Rajani R, Cheng VY, *et al.* Increase in epicardial fat volume is associated with greater coronary artery calcification progression in subjects at intermediate risk by coronary calcium score: a serial study using non-contrast cardiac CT. *Atherosclerosis* 2011; 218: 363–368.
- 11 Wassel CL, Laughlin GA, Araneta MR, *et al.* Associations of pericardial and intrathoracic fat with coronary calcium presence and progression in a multiethnic study. *Obesity (Silver Spring)* 2013; 21: 1704–1712.
- 12 Smilde TJ, van Wissen S, Wollersheim H, *et al.* Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. *Lancet* 2001; 357: 577–581.
- 13 Howard BV, Hsia J, Ouyang P, *et al.* Postmenopausal hormone therapy is associated with atherosclerosis progression in women with abnormal glucose tolerance. *Circulation* 2004; 110: 201–206.
- 14 Nair GV, Waters D, Rogers W, *et al.* Pulse pressure and coronary atherosclerosis progression in postmenopausal women. *Hypertension* 2005; 45: 53–57.
- 15 Shukla A, Sharma MK, Jain A, *et al.* Prevention of atherosclerosis progression using atorvastatin in normolipidemic coronary artery disease patients—a controlled randomized trial. *Indian Heart J* 2005; 57: 675–680.
- 16 Rodriguez-Granillo GA, Vos J, Bruining N, *et al.* Long-term effect of perindopril on coronary atherosclerosis progression [from the perindopril's prospective effect on coronary atherosclerosis by angiography and intravascular ultrasound evaluation (PERSPECTIVE) study]. *Am J Cardiol* 2007; 100: 159–163.
- 17 Gibson AO, Blaha MJ, Arnan MK, *et al.* Coronary artery calcium and incident cerebrovascular events in an asymptomatic cohort. The MESA Study. *JACC Cardiovasc Imaging* 2014; 7: 1108–1115.
- 18 Kavousi M, Elias-Smale S, Rutten JH, *et al.* Evaluation of newer risk markers for coronary heart disease risk classification: a cohort study. *Ann Intern Med* 2012; 156: 438–444.
- 19 Newman AB, Naydeck BL, Ives DG, *et al.* Coronary artery calcium, carotid artery wall thickness, and cardiovascular disease outcomes in adults 70 to 99 years old. *Am J Cardiol* 2008; 101: 186–192.
- 20 Rajsheker S, Manka D, Blomkalns AL, *et al.* Crosstalk between perivascular adipose tissue and blood vessels. *Curr Opin Pharmacol* 2010; 10: 191–196.
- 21 Mazurek T, Zhang L, Zalewski A, *et al.* Human epicardial adipose tissue is a source of inflammatory mediators. *Circulation* 2003; 108: 2460–2466.