PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Hou, Jingjing; Li, Moran; Han, Jun; Yu, Shikai; Jia, Xinming; Sun, Fenyong; Zhang, Yi

VERSION 1 – REVIEW

REVIEWER	Bijani, Mostafa Fasa University of Medical Science, Department of Medical Surgical Nursing, Fasa University of Medical Sciences, Fasa, Iran
REVIEW RETURNED	19-May-2023

GENERAL COMMENTS	Thanks to the respected editor for the opportunity to review the article. The topic of the article is very interesting and practical. The article is well written, but to improve the quality of the study, the following amendments seem necessary 1. In the method section of sampling type, the formula for calculating the sample size and the diagram of the sampling method should be added 2- The discussion section is written very briefly and does not have good coherence. It is necessary for the respected author to develop the discussion section and structure the discussion section based on the findings of the study. What is the application of study findings in the clinical practice?

REVIEWER	Monte, Marco Angelo University of Catania
REVIEW RETURNED	24-Jul-2023

GENERAL COMMENTS	In the manuscript entitled “Assessment of early cardiovascular organ damage and disease management: study protocol of the North Shanghai Study II” the Authors prospectively manage to evaluate the phenotypes of early cardiovascular organ structural and functional damage in Chinese population through a digital follow-up. The rationale is fully relevant for the development of future cardiovascular prevention strategies. However, I must admit that I have some major concerns: 1. The evaluation of myocardial injury relies upon enzymes whose diagnostic capabilities have been largely supplanted by high-sensitivity troponin assays (HS-Tn), which are not mentioned in the study protocol. Obtaining values of HS-Tn would be a valuable contribution to the correct classification of myocardial damage. 2. Exclusion criteria (among the other) are represented by: NYHA class IV, CKD > 3, history of stroke within 3 months. Of course, patients with milder symptoms of heart failure (e.g., NYHA class

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	III), CKD = 3, or stroke beyond 3 months are considerable as enrollable in the study. As the main objective of the study stems on the identification of early cardiovascular organ structural and functional damage rather than the late one, the eligibility criteria do not completely fulfill the purpose. As such, patients with established cardiovascular damage should be excluded. 3. The way the patients will undergo the two clinical pathway (A and B) is not very clear. 4. The overall duration of the long-term follow-up is not clearly stated, as it may hardly impact on the overall results. Moreover, I have some minor suggestions: 1. There are several grammatical and lexical errors, please double check. 2. The characteristics of the “electronic bank” through which data will be stored and then evaluated are not well explained.

VERSION 1 – AUTHOR RESPONSE

Response to the reviewers’ comments:
Reviewer #1:
1.In the method section of sampling type, the formula for calculating the sample size and the diagram of the sampling method should be added
Response:Many thanks for your comment and suggestion.Our study aims to establish a prospective cohort for the assessment of early cardiovascular organ damage, there is no clear distinction between exposure and non exposure. In addition, the study is an all- comers register study,so the sampling method diagram is not included in the article. The specific calculation method is supplemented in the “Sample size calculation” section of the article “Method”,as seen in Page 5 Line 15.
Sample size calculation
By querying data and referring to the queue of North 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:
n=
P is the overall rate, δ is allowable absolute error, α= 0.05,=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 enrollment target is 4000-5000 cases.
2.The discussion section is written very briefly and does not have good coherence. It is necessary for the respected author to develop the discussion section and structure the discussion section based on the findings of the study.
Response:Many thanks for your constructive suggestions. We have made new modifications to the discussion section. Now it mainly includes the necessity, significance, expected findings,and current limitations of the research.As follows:
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 tumors 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

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similar risk factors, such as genetics, advanced age, smoking, obesity, hypertension, and diabetes. The 5-year survival rate of malignant tumors is 40%, and the 5-year survival rate of cardiovascular diseases such as heart failure is only 50%.At present, a series of preventive precancer screening programs have been established for tumors, 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 as well.

Asymptomatic early organ damage is the early stage of cardiovascular disease, which is similar to precancerous lesions of tumors. 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 labeled 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 35the 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 developed, and its implementation in clinical practice is anticipated to guide clinical decisions.In other words, there will not only be models to evaluate the level of lifestyle health, such as exercise habits, body mass index,smoking and drinking habits, but scores for early organ damage can also be obtained, this will enable us to gain an understanding of a patient's cardiovascular health status, and thus allow us to create tailored treatment plans. Consequently, through offering early prevention and treatment measures,we can reduce the risk of developing cardiovascular disease, minimize the potential for negative medical outcomes and, ultimately, improve patients' quality of life going forward.

By comprehensively detecting early organ damage, we may provide assistance in identifying potential drugs that can improve cardiovascular early organ damage and protect patient target organ function.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 randomized, 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, stabilize high-risk plaques, and even cause plaque reversal, providing clinical benefits.

And the biobank for early cardiovascular organ damage in the Chinese population, including blood, urine, feces,DNA and all data will be uniformly stored, managed, updated by a dedicated person authorized by the researchers, and automatically generated into a unified digital report.This examination report may continue to be used in future intervention studies.

In summary, we intend to create a prospective cohort based on a Chinese population, with a focus on the standardized and traceable assessment of early cardiovascular organ damage. However, some of the measurements necessitate specialized equipment, which may not be available in certain regions and populations. 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(e.g., 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(e.g., NYHA IV) .

What is the application of study findings in the clinical practice?

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Response:Thank you very much for raising such an important question. Actually,the fact of this paper describes a study protocol, not a research paper with findings of the study. Hence,we have revised the discussion more to comment on the “expected” findings of the study.As seen in Page 17 Line 4,as follows:

DISCUSSION

In the future, a cardiovascular risk assessment and prediction model based on early organ damage will be developed, and its implementation in clinical practice is anticipated to guide clinical decisions.In other words, there will not only be models to evaluate the level of lifestyle health, such as exercise habits, body mass index,smoking and drinking habits, but scores for early organ damage can also be obtained, this will enable us to gain an understanding of a patient's cardiovascular health status, and thus allow us to create tailored treatment plans. Consequently, through offering early prevention and treatment measures,we can reduce the risk of developing cardiovascular disease, minimize the potential for negative medical outcomes and, ultimately, improve patients' quality of life going forward.

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Reviewer #2:

1.The evaluation of myocardial injury relies upon enzymes whose diagnostic capabilities have been largely supplanted by high-sensitivity troponin assays (HS-Tn), which are not mentioned in the study protocol. Obtaining values of HS-Tn would be a valuable contribution to the correct classification of myocardial damage.

Response: We appreciate your comments and agree with you. The term “myocardial enzyme” evaluation is not appropriate. I have revised it to “Myocardial injury biomarkers” in the article, including sensitive troponin (hs-Tn) and other myocardial enzymes. This part of the error has been corrected in the article, as seen in Page 11 Line 21.

Myocardial injury biomarkers

Extract 2-3 ml of venous blood from participants for blood biochemical testing. The main biochemical markers of myocardial ischemic 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 complete marker report, issued by the Laboratory Department of Shanghai Tenth People's Hospital will ultimately be obtained, which has important value in determining the time and severity of myocardial injury and correctly classifying myocardial injury.

2. Exclusion criteria (among the other) are represented by: NYHA class IV, CKD > 3, history of stroke within 3 months. Of course, patients with milder symptoms of heart failure (e.g., NYHA class III), CKD = 3, or stroke beyond 3 months are considerable as enrollable in the study. As the main objective of the study stems on the identification of early cardiovascular organ structural and functional damage rather than the late one, the eligibility criteria do not completely fulfill the purpose. As such, patients with established cardiovascular damage should be excluded.

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Response:We strongly agree with the reviewer's point of view, but as an all-comers prospective population study, considering the sample size of enrollment, we hope to study the impact of some organ damage on terminal events in patients without or with milder cardiovascular disease((e.g., NYHA ≤ III)). We did not rule out some milder vascular diseases, such as early coronary heart disease or TIA, and excluded some patients with very serious cardiovascular and cerebrovascular diseases. Considering the reviewer's suggestions, we have included our considerations in theDISCUSSION,and put it in the STRENGTHS AND LIMITATIONS.Thanks again for your time and contribution to this article.As seen in Page 2 Line 28, and in DISCUSSION(Page17 Line28-30 and Page 18 Line 1-3) .

STRENGTHS AND LIMITATIONS

The most desirable situation would be to analyze 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.

DISCUSSION

In summary, we intend to create a prospective cohort based on a Chinese population, with a focus on the standardized and traceable assessment of early cardiovascular organ damage. However, some of the measurements necessitate specialized equipment, which may not be available in certain regions and populations. 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(e.g., 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(e.g., NYHA IV) .

3. The way the patients will undergo the two clinical pathway (A and B) is not very clear.

Response:Thank you for your critical comment. The two clinical pathways are two sets of tests for participants to choose from, and their difference lies only in the number of tests. After carefully considering your opinion, we have revised the original two clinical pathways A and B, replacing them with a more logical presentation from the perspectives of risk factors assessment and organ damage assessment.As seen in Page 6 Line 13-Page 13 Line 26.

4. The overall duration of the long-term follow-up is not clearly stated, as it may hardly impact on the overall results.

Response:Many thanks for your constructive comments and suggestions. And we have added it in the section of Study outcomes and follow-up,as seen in Page 14 Line 25.Table 3 can also provide a good explanation.

Study outcomes and follow-up

The primary endpoint of this study is the composite of major adverse cardiovascular events (MACE) , including cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, or revascularization ((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 magnetic resonance imaging. Non-fatal myocardial infarction is characterized by typical chest pain symptoms and/or characteristic electrocardiogram changes with troponin I > 1.0 ng/mL or troponin T > 0.1 ng/mL. Coronary artery revascularization 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 hospitalization 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 (CKD3 period), or increased microalbuminuria;(2)newly diagnosed cardiovascular or cerebrovascular diseases(including newly diagnosed hypertension, transient ischemic attack,etc),or newly diagnosed renal insufficiency with proteinuria, or newly diagnosed diabetes.

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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.
Moreover, I have some minor suggestions:
1. There are several grammatical and lexical errors, please double check.
Response: We are truly sorry for these language errors .We have checked and corrected.
2. The characteristics of the “electronic bank” through which data will be stored and then evaluated are not well explained.
Response:Thank you again for your valuable suggestions.This issue is very important, and it is our next research plan, so we did not submit it specifically. Based on your suggestion, we have added ideas for digital reports and future intervention research during the discussion process,as seen in Page 17 Line 21.
DISCUSSION
And the biobank for early cardiovascular organ damage in the Chinese population, including blood, urine, feces,DNA and all data will be uniformly stored, managed, updated by a dedicated person authorized by the researchers, and automatically generated into a unified digital report.This examination report may continue to be used in future intervention studies.

VERSION 2 – REVIEW

REVIEWER	Monte, Marco Angelo University of Catania
REVIEW RETURNED	24-Oct-2023

GENERAL COMMENTS	In the new version of the manuscript, the Authors addressed the evaluation of myocardial injury and clearly stated the study protocol. The language has shown improvement, although there is still potential for further enhancement. Moreover, the Authors clearly explained the reasons for the exclusions criteria, considering the possibility of extending opportunistic screening also to a population with a higher risk compared to population with a clear absence of organ damage.

VERSION 2 – AUTHOR RESPONSE

Response to the reviewers’ comments:

Reviewer : 2

In the new version of the manuscript, the Authors addressed the evaluation of myocardial injury and clearly stated the study protocol. The language has shown improvement, although there is still potential for further enhancement. Moreover, the Authors clearly explained the reasons for the exclusions criteria, considering the possibility of extending opportunistic screening also to a population with a higher risk compared to population with a clear absence of organ damage.

Response: Many thanks for your constructive comments and nice summary on our study. And we have modified some language expressions in the article.

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