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Computed tomography screening for early lung cancer, COPD and cardiovascular disease in Shanghai: Rationale and design of a population-based comparative study

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Abstract

Rationale and Objectives: To describe the rationale and design of a population-based comparative study. The objective of the study is to assess the screening performance of volume-based management of CT-detected lung nodule in comparison to diameter-based management, and to improve the effectiveness of CT screening for COPD and CVD, in addition to lung cancer, based on quantitative measurement of CT imaging biomarkers in a Chinese screening setting.

Materials and Methods: A population-based comparative study is being performed, including 10,000 asymptomatic participants between 40 and 74 years old from Shanghai urban population. Participants in the intervention group undergo a low-dose chest and cardiac CT scan at baseline and one year later, and are managed according to NELCIN-B3 protocol. Participants in the control group undergo a low-dose chest CT scan according to the routine CT protocol and are managed according to the clinical practice. Epidemiological data are collected through questionnaires. In the fourth year from baseline, the diagnosis of the three diseases will be collected.

Results: The unnecessary referral rate will be compared between NELCIN-B3 and standard protocol for managing early-detected lung nodules. The effectiveness of quantitative measurement of CT imaging biomarkers for early detection of lung cancer, COPD and CVD will be evaluated.

Conclusion: We expect that the quantitative assessment of the CT imaging biomarkers will reduce the number of unnecessary referrals for early detected lung nodules, and will improve the early detection of COPD and CVD in a Chinese urban population.

Trial registration: ClinicalTrials.gov, NCT03988322. Registered on 14 June 2019.

Keywords: lung cancer, chronic obstructive pulmonary disease, cardiovascular disease, biomarkers, screening, computed tomography

Introduction

Lung cancer, Chronic Obstructive Pulmonary Disease (COPD) and Cardiovascular Disease (CVD), so-called Big-3 diseases, are primary causes of death in China¹. The Chinese Cancer Center reported that **lung cancer** was the most common cause of cancer incidence and cancer-related death in 2014, with 780 thousand new cases of both lung cancer and 630 thousand deaths². COPD and CVD are the two leading causes of death in China³. **COPD** accounted for more than 910 thousand deaths in 2013¹. According to the latest national study, COPD is highly prevalent (13.6%) in individuals aged 40 years and older, indicating a substantial public-health problem⁴. **CVD** accounted for about 3.5 million deaths (about 40% of all deaths) in 2016 based on the national CVD report in China⁵.

Behavior-related factors, including smoking, unhealthy diet and physical inactivity, and air pollution are the leading risk factors for the Big-3 diseases and related mortality in China³. According to the 2015 China Adult Tobacco Survey, there are 316 million smokers in China, with a smoking rate of 27.7% for adults (52.1% for men and 2.7% for women). As estimated, the population attributable fraction of smoking and lung cancer death was 44.7% for men and 6.4% for women in 2014⁶. Studies showed that at least 20 pack-years of cigarette smoking is associated with around 2-fold increased risk of COPD⁷, and has a remarkable combined effect with hypertension on the risk of CVD-related mortality⁸. Physical activity shows a significantly protective effect against both lung cancer and CVD³. An unhealthy diet increases the risk of COPD and is associated with a higher risk of cardiovascular mortality³.

Low-dose chest computed tomography (CT) is considered as a screening method for early detection of lung cancer in the population at risk⁹, and it can also be used to detect COPD and CVD^{10,11}. Early detection followed by early management could delay or stop the progression of the Big-3 diseases, by providing therapy at a treatable stage in many patients¹²⁻¹⁴. The national and local CT screening programs in China are mainly focusing on detecting lung cancer, in which diameter assessment of detected lung nodules is adopted^{15,16}. One of the major controversies surrounding diameter-based low-dose CT lung cancer screening is the high false-positive rate¹⁷, resulting in unnecessary workup. Studies from the NELSON trial showed the benefit of quantitative assessment of CT screening-detected lung nodules. Namely,

volume-based management for lung nodules is associated with a far lower rate of unnecessary referral as compared to diameter-based management, with a comparable lung cancer detection rate in a European population¹⁸. Besides, a review indicated that screening for COPD and CVD, in addition to lung cancer, may significantly increase the benefits of low-dose CT lung cancer screening¹⁹. Given the large disease burden caused by the Big-3 in China, a developing country with limited medical resources²⁰, introducing quantitative CT screening for Big-3 diseases could have a positive impact on the Chinese healthcare and society by reducing the rate of unnecessary referrals for further investigation in terms of lung nodules detection and increasing screening benefits.

To our knowledge there has been no study looking at volumetric measurement and management of lung nodules detected by low dose CT screening, and the combined CT screening for lung cancer, COPD and CVD in a Chinese population. Our research team initiated a comparative study to address the gap in knowledge. With regards to the lung cancer CT screening, the primary hypothesis is that the volume-based lung nodule management will be associated with a lower rate of unnecessary referral for further investigation as compared to the currently used diameter-based management in a Chinese population. Secondary goals are to improve the effectiveness of population CT screening for the Big-3 diseases by (1) proposing optimized cut-off values of quantitative CT imaging biomarkers for Chinese population; and (2) identifying risk factors associated with the Big-3 diseases in early stages to optimize the eligibility criteria for people who would benefit most from CT screening.

Materials and Methods

This study is embedded in the NELCIN-B3 project, which involves three large hospitals in China²¹ and an academic hospital in the Netherlands . This paper focuses on the study design in the leading hospital, one of the three involved hospitals in China. Due to different set up and procedures in all four hospitals, it is not feasible to fit the description of the design and anticipated results in a single manuscript. The design of the NELCIN-B3 project is based on findings and expertise obtained from two large-scale Dutch (-Belgian) projects: The Dutch-Belgian Randomized Lung Cancer Screening Trial (Dutch acronym: NELSON)¹⁸ and the Risk Or Benefit IN Screening for Cardiovascular disease (ROBINSCA) study²². In the abovementioned studies, innovative low-dose CT protocols for screening and management of early lung cancer and CVD were developed. To validate the findings in a Chinese setting, and importantly, to optimize the criteria for CT screening in China where lung cancer, COPD and CVD are highly prevalent, the Chinese research team together with the Dutch research team initiated the screening for lung cancer, COPD and CVD by low-dose CT (Netherlands-China Big-3 screening: NELCIN-B3).

Study design

A population-based comparative study is being performed among 10,000 individuals from the general urban population in Shanghai, China. In total, 5,000 participants in the intervention group undergo a low-dose chest and cardiac CT scan at baseline and one year after baseline. They are managed according to the NELCIN-B3 protocol with regards to imaging biomarkers of lung cancer, COPD, and CVD. The 5,000 participants in the control group undergo a low-dose chest CT at baseline and one year after baseline according to the routine CT protocol used in the hospital, and are managed according to the standard clinical practice. Participant reported data and clinical data are collected at baseline, one-year follow up and in the fourth year from baseline visit. The performance of the two protocols for lung nodules management will be assessed and compared in terms of unnecessary referral rate. The unnecessary referral is defined as the referral for further examination (e.g. biopsy or surgery or follow-up CT examination) in case of false positive results and indeterminate results that

eventually turns out to be negative. In addition, the performance of quantitative CT imaging biomarkers for early detection of Big-3 diseases will be assessed. The study also allows identifying the risk factors associated with the Big-3 diseases in early stages to optimize the eligibility criteria for people who would benefit most from CT screening. Figure 1 presents an overview of the study design.

Participants

Inclusion criteria for participants are: 1) asymptomatic (without complaints of chest discomfort) residents registered in Shanghai city, 2) age between 40-74 years old, and 3) no history of lung cancer (self-reported). Pregnant women are excluded. Inclusion criteria are assessed by a doctor in a Community Health Service Center (CHSC) during a face-to-face interview using a questionnaire.

Eligible participants have been recruited from 10 communities in Huangpu District, Shanghai City and the health check center of leading hospital (ongoing). Five thousand participants in the intervention group are recruited from the 10 communities in Huangpu District starting from September 2018 (ongoing). Five thousand participants in the control group are recruited from the health check center starting from March 2018 (ongoing).

A recruitment campaign in the communities has been launched in July 2018 by using information posters, leaflets and the official WeChat account of each CHSC, and is ongoing. The researcher group in leading hospital has trained the staff in how to introduce the project, recruit participants and fill in the questionnaires. The trained staff in CHSC mobilizes residents to participate by distributing leaflets.

CT scan and management of imaging biomarkers for Big-3

The parameter settings of the CT scan, data collected from the CT scan and the management of imaging biomarkers of the Big-3 diseases in the intervention and control group are summarized in Table 1.

Intervention group

CT image acquisition and reconstruction

Participants in the intervention group are screened with a low-dose CT at the Department of Radiology in the leading hospital. A 256-slice CT system (Brilliance iCT, Philips Healthcare, The Netherlands) is used to obtain CT images according to the NELCIN-B3 CT scan protocol. This CT protocol is developed for quantitative assessment of lung nodules, COPD and Coronary artery calcium (CAC), based on established CT protocols of the NELSON and ROBINSCA trials^{18, 22}. Acquisition and reconstruction parameters for chest and cardiac CT scans are reported in appendix Table S1 and Table S2.

Image analysis

The CT images are being read using the Philips intelligispace portal (version 8) workstation by radiologists. The volume and other phenotypical features of lung nodules and COPD and quantitative measurements for all three diseases are collected. A previous analysis from the NELSON study showed no benefit of consensus double reading at baseline screening versus single reading²³. In this study, the necessity of double reading will be tested in a pilot study including 2,000 participants in the intervention group. If consensus double reading shows no benefit in this study either, then one trained radiologist will continue to read the consecutive scans.

Lung nodules management

Solid and part-solid nodules

Detected solid and part-solid lung nodules (visible in a mediastinal window setting) are managed according to the European volume-based protocol, based on the volume and volume doubling time (VDT) of lung nodule (Figure 2)⁹. In short, solid and part-solid lung nodules are classified into three groups depending on nodule volume: $< 100 \text{ mm}^3$ (negative result), $100\text{-}300 \text{ mm}^3$ (indeterminate result) and $> 300 \text{ mm}^3$ (positive result). For part-solid nodules, only the solid component is measured. In case of a negative result, a CT scan after one year is recommended. In case of an indeterminate result, a 3-month follow up CT is recommended at which VDT will be assessed. For short VDT (< 400 days), the screening result is positive. Long VDT (> 400 days) is considered a negative screening result. In case of a positive result, referral to a multidisciplinary team is recommended for further investigation⁹. In the second

round CT scan, in case of nodules that have been detected previously, the second round result will be based on the VDT and managed according to category at 3 months.

Non-solid nodules

There is currently no validated management for non-solid nodules based on the assessment of volume and VDT. Therefore, in the intervention group, the management is performed according to the standard diameter-based protocol as in the control group. Participants with a pure ground glass nodule (pGGN) with a diameter ≥ 20 mm undergo 6-month follow-up chest CT scan, while participants with a smaller pGGN undergo the second round chest CT scan after one year from the baseline (see the detailed description in control group). The volume and mass of pGGN are registered for each CT scan where applicable, and VDT and mass doubling time will be calculated.

Incidental solid and part-solid nodules at follow-up

Incidental nodules can be detected at 3-month follow-up scan and/or second round scan. The volume of the solid nodules and the solid component of part-solid nodules are measured. They are managed according to the European volume-based protocol⁹. This protocol recommends a second round CT scan for nodule volume $< 30\text{mm}^3$ (negative result), 3-month follow up CT scan for nodule volume $30\text{-}200\text{mm}^3$ (indeterminate result), and referral for further work-up for nodule volume $\geq 200\text{ mm}^3$ (Figure 3).

COPD management

The low-dose inspiratory chest CT scan is assessed for emphysema and airway disease. The emphysema index, which is defined as the percentage of lung voxels less than -950 HU at inspiratory CT, will be automatically calculated. The airway disease is evaluated by using CT measurements of airway wall thickness (WT), luminal diameter (LD), and airway wall area percent (WA%). The phenotypes of the emphysematous destruction and airway changes are classified according to the modified Fleischner criteria²⁴. The detected emphysema and/or bronchial wall thickness are recorded in the CT report and lifestyle advice like smoking cessation and avoiding respiratory tract infections is suggested. Lung function is also tested for each participant (described later). If the ratio of forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) is less than 0.70, the corresponding CHCSs and

general practitioners are informed. The general practitioners diagnose and manage COPD according to the GOLD guideline²⁵.

Coronary artery calcium management

The electrocardiographic-triggered cardiac CT scan is evaluated for coronary artery calcium, according to the Agatston method. Cardiovascular risk stratification is performed based on the Agatston score²². CAC is categorized into three groups depending on Agatston score: < 100 (low), 100 - 399 (medium) and ≥ 400 (high). In case of medium and high risk of cardiovascular disease, a participant is referred to the general practitioners in the respective CHCSs. In the 4-year follow-up period, any diagnosis of CVD in participants, if applicable, will be based on current local CVD guidelines.

Control group

CT image acquisition and reconstruction

Participants in the control group undergo a CT screening at the Department of Radiology and Outpatient Clinic in the leading hospital. The scans are performed using a Philips 64 MDCT system (Ingenuity 64, Philips medical systems, the Netherlands) according to standard scan protocol (Table S1). The standard hospital protocol is routinely used for visual assessment of the chest and diameter-based evaluation of lung nodules. Positioning of participants is head-first, supine, arms above the head. The chest CT image acquisition is performed at inspiration. Scanning parameters are as follows: (a) spiral scan mode with 120 kVp and a reference tube current of 50 mAs. (b) two reconstruction kernels are performed, lung algorithm and mediastinal algorithm.

Image analysis

One resident radiologist evaluates the CT images using Philips intellispace portal (version 8) workstation with a supervising radiologist. The diameter and other phenotypical features of

lung nodules are registered. The qualitative assessment of emphysema, bronchial wall thickness and CAC is performed.

Lung nodule management

Detected lung nodules are managed according to the standard protocol used in the hospital, the NCCN Clinical Practice Guideline in Oncology for Lung Cancer Screening, Version 2.2018-August 8, 2017²⁶. This guideline recommends management of lung nodules based on their diameter.

Participants without lung nodules or with a solid or part-solid nodule ≤ 5 mm undergo a second round chest CT scan 1 year after baseline. Participants with a solid nodule 6-7 mm or part-solid nodule ≥ 6 mm with solid component ≤ 5 will undergo follow-up chest CT 6 months after baseline. Participants with a solid nodule 8-14 mm or part-solid nodule ≥ 6 mm with solid component within 6-7 mm undergo follow-up chest CT 3 months after baseline. Participants with a solid nodule ≥ 15 mm or part-solid nodule with solid component ≥ 8 mm are referred to a multidisciplinary team for clinical investigation and, if applicable, treatment.

Participants with a non-solid nodule ≤ 19 mm undergo a second round chest CT scan one year after baseline. Participants with a non-solid nodule ≥ 20 mm are recommended to undergo 6 months follow up CT scan.

Participants with an incidental solid nodule ≥ 8 mm or part-solid nodule with solid component ≥ 4 mm or non-solid nodule ≥ 20 mm are referred to a multidisciplinary team for clinical investigation and, if applicable, treatment. Participants with smaller-size incidental nodules are recommended to undergo a, 3-month follow-up or 6-month follow-up or second-round CT scan as described in the NCCN guideline²⁶.

Coronary artery calcium and COPD management

Detected CAC, emphysema and/or bronchial wall thickness are qualitatively recorded in the CT report but no suggestions are given for management. The CHSCs and the general practitioners are not informed, as it is in current routine practice.

Physical examination, laboratory measurements and participant reported data

A number of participants' characteristics are collected in order to identify risk factors associated with the Big-3 imaging biomarkers and to optimize the eligibility criteria for people who would benefit most from CT screening. For the intervention group, the following data are collected at baseline and one year after the baseline: values of physical examination (weight, height, blood pressure, lung function), values of laboratory measurements (fasting plasma glucose, total cholesterol, HDL-cholesterol, triglycerides, serum potassium, and urine albumin/creatinine ratio). Weight, height and blood pressure are measured at CHSCs. Lung function test will be performed at the Department of Radiology in the leading hospital using Multi-Functional Spirometer HI-801. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and FEV1/FVC ratio (FEV1%) will be assessed. The laboratory test is performed in CHSCs or a third-party institute. One year after the baseline, participants in the intervention group will be approached again to collect data on physical examination and laboratory measurements.

In addition, trained staffs in CHSCs fill in questionnaires during face-to-face interviews with each participant in both the intervention and control groups at baseline. The questionnaires contain general characteristics (age, sex, education, employment status, and socio-economic status), risk factors of Big-3 diseases, and health status of the participants. The following questionnaires are used for the interview: (1) Questionnaire intended for data collection about general characteristics of participants, medical history, known risk factors of lung cancer including behavioral, environmental and occupational risk factors; (2) Symptom-based questionnaire for screening COPD²⁷; (3) Rose chest pain questionnaire²⁸; and (4) EQ5D-3L questionnaire²⁹. One year after the baseline, participants in the both groups will be approached again to collect data on participant reported modified risk factors of Big-3 and overall health status to detect the changes in behavior and health status.

In the fourth year from baseline visit, the diagnosis of lung cancer, COPD, CVD and related treatment for all participants will be collected through the Hospital Information System (HIS) of leading Hospital and from the GPs.

Quality assurance of data collection

Various quality control measures are taken at each step to ensure the quality of data collection:

1) technical quality monitoring of CT image acquisition is provided by specialized technician from leading hospital and Philips firm; 2) to ensure the quality of image analysis, necessity of double reading for consensus will be evaluated in a side study; 3) all the staff involved to the project was formally trained by the researchers from leading hospital; 4) an appropriate software for data management was prepared, especially designed to ease the data entry process. A team of trained staff is entering the data under the supervision of senior researchers. Five percent of the entered data will be double checked by senior researchers for quality assurance.

Confidentiality and storage

All personal identification information of participants is removed from the dataset (name, participant number, date of birth, et al). Data for the study is recorded by the radiologist who is on duty every day on a day of data entry. In accordance to the Cybersecurity Law in China, the source data (paper questionnaires and laboratory samples) have to be stored in leading hospital and the CT images for the research are separately stored in the Picture Archiving and Communication Systems (PACS) (Winning Health Technology Group Co., Ltd) in the hospital.

Power analysis

The power is calculated based on the primary outcome. A previous analysis from the NELSON study showed that the volume-based protocol for lung nodules detection results in an unnecessary referral rate of 12% and for the diameter-based protocol in a rate of 27%¹⁸. These numbers were used to estimate the effect size of the volume-based protocol in Chinese population. With an effect size of 0.46, a sample size of 10,000 and an alpha error of 5 percent, the study will have more than 95 percent power to detect the effect of the NELCIN protocol on the referral rate of lung nodules compared to the standard protocol.

Results

The unnecessary referral rate (number of unnecessary referrals divided by total participants) for detected lung nodules in the groups of NELCIN-B3 protocol and standard protocol will be calculated and compared. The detection rate of lung cancer, COPD and CVD at baseline in the intervention and control groups will be compared, and the incidence rate of the Big-3 diseases during the follow-up will be compared. The cut-off value of quantitative imaging biomarkers for early detection of Big-3 diseases will be explored. Relevant risk factors related to the presence of CT imaging biomarkers for Big-3 diseases will be identified. The data collection is ongoing and the results will be revealed once the baseline screening is finalized.

Discussion

Low-dose CT has been widely recognized and studied for lung cancer screening since the National Lung Screening Trial (NLST) in the United States demonstrated that low-dose CT screening decreased lung cancer mortality by 20% compared to radiography¹². The *Cardiothoracic Group of Radiology Branch in Chinese Medical Association* and *Chinese Lung Cancer Early Diagnosis and Treatment Group* have developed and modified Chinese guidelines and expert consensus statements for CT lung cancer screening accordingly^{30,31}, where lung nodules management is described based on nodule diameter. Study showed the benefit of volume-based management of lung nodules in terms of a much lower false positive rate compared to diameter-based management¹⁸ and volumetric assessment of lung nodules is efficient in comparison to diameter assessment in Europe³². This study is intended to test whether the volume-based management will also show a better performance in terms of unnecessary referral rate in a Chinese setting, where non-smoking related lung cancer is much more frequent compared to Europe³³.

CT screening for COPD in asymptomatic adults is not routinely recommended³⁴. In the last two decades, improvements in CT technique and post-processing software have allowed quantitative evaluation of COPD. Studies showed that quantitative imaging biomarkers of emphysema and bronchial wall thickness obtained with low-dose CT at lung cancer screening might be useful for early diagnosis of COPD³⁵. However, little is known about identification of COPD by imaging biomarkers in a Chinese population. In this study, we will evaluate if CT imaging biomarkers for COPD add to the diagnostic ability of the routinely used lung function test for early detection of COPD in Chinese population.

According to the guideline from ACCF/AHA (American College of Cardiology Foundation/American Heart Association), measuring CAC with CT may be useful among asymptomatic adults having at least intermediate risk of cardiovascular disease³⁶. Studies, including those where ROBINSKA researchers were involved, showed that CAC score measured with CT improves cardiovascular risk prediction in Caucasians^{37,38}. In the Multi-

Ethnic Study of Atherosclerosis (MESA) study, CAC was not predictive of major coronary event among Chinese participants in the United States³⁸. However, this finding was limited by the few events in Chinese participants in that study. This study could show the impact of CAC value in cardiovascular risk prediction in Chinese screening setting as compared to traditional risk factors³⁹.

Given the above issues on early detection of Big-3, the NELCIN-B3 project has the following advantages. First, a volume-based protocol for lung nodule management will be applied in Chinese screening setting for the first time, which is expected to reduce the number of unnecessary follow-up tests and the false-positive rate in a Chinese population. Second, the quantitative CT imaging biomarkers for COPD and CVD will be assessed for early detection, increasing the potential benefits of CT screening for lung cancer. Third, implementation of quantitative imaging biomarkers combined with lung function test and laboratory measurements could help to optimize the early detection and management of the Big-3 diseases in China. The international collaboration and shared experience in this project extend the expertise of the research team and are expected to yield promising results.

The study has some limitations. First, the management of non-solid nodules in the intervention group will be based on the diameter because of lack of validated volume-based protocol. The volume and mass of non-solid nodules will be carefully evaluated at each screening round in relation to the final clinical outcome after follow-up. Second, data on physical examination and laboratory measurements will only be collected for the intervention group, so the added value of them can only be evaluated in that group.

In conclusion, we expect that the findings of this study will improve the effectiveness of population-based CT screening for early detection of lung cancer, COPD and CVD.

Dissemination

The findings of this study will be disseminated through peer-reviewed publications and presented at national and international conferences.

Ethics approval and consent to participate

This study will be performed by the leading hospital in China of NELCIN-B3 project and is a part of the NELCIN-B3 project. The study adheres to the Declaration of Helsinki. The ethical approval for NELCIN-B3 project was issued by the Biomedical Research Ethics Committee of leading institute. Each participant will be asked to read and sign the informed consent form, which introduces the screening project, benefits, potential harms and confidentiality.

Role of the Funding Source

The funding sources had no role in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

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Competing interest

Prof. M Oudkerk discloses that he holds a financial interest in iDNA - the Institute for Diagnostic Accuracy Research BV, an organization that aims to speed up the global implementation of the early detection of lung cancer (with comorbidities in cardiovascular diseases and COPD). The other authors declare that they have no competing interests.

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Table 1 Summary of CT scan protocol and management of imaging biomarkers for lung cancer, COPD and CVD in the intervention and control groups

	Intervention group	Control group
Round of CT scan	Two rounds of CT scan (baseline and one year after baseline) in 4 years	Two rounds of CT scan (baseline and one year after baseline) in 4 years
CT image acquisition	A 256-slice CT system (Brilliance iCT, Philips Healthcare, The Netherlands) with pre-defined scanning parameters	Philips 64 MDCT system (Ingenuity 64, Philips medical systems, the Netherlands) with routine scanning parameters
Field of View (FOV)	Chest and cardiac	Chest
Reconstruction	4 reconstructions for chest and 2 reconstructions for cardiac	2 reconstructions for chest
Image analysis	Philips intelligispace portal (version 8) workstation	Philips intelligispace portal (version 8) workstation
Parameters collected	The volume of lung nodules, other phenotypical features of lung nodules and COPD and quantitative measurements for all three diseases.	The diameter and other phenotypical features of lung nodules. The qualitative assessment of emphysema, bronchial wall thickness and coronary artery calcium.
Management of detected imaging biomarkers		
Lung nodule	European volume-based protocol	NCCN (diameter-based)
COPD(emphysema and/or bronchial wall thickness)	Lifestyle advice (smoking cessation and avoiding respiratory tract infections). Referral to general practitioner in case of positive result of lung function test	No suggestions and no referral as it is in current routine practice No suggestions and no referral as it is in current routine practice
Coronary artery calcium	Referral to general practitioner in case of medium and high risk of cardiovascular disease	is in current routine practice
Data collected in the 4th year from baseline visit	The diagnosis of lung cancer, COPD and CVD	The diagnosis of lung cancer, COPD and CVD

Figure legends

Figure 1. Study design of computed tomography screening for early lung cancer, COPD and cardiovascular disease in Shanghai

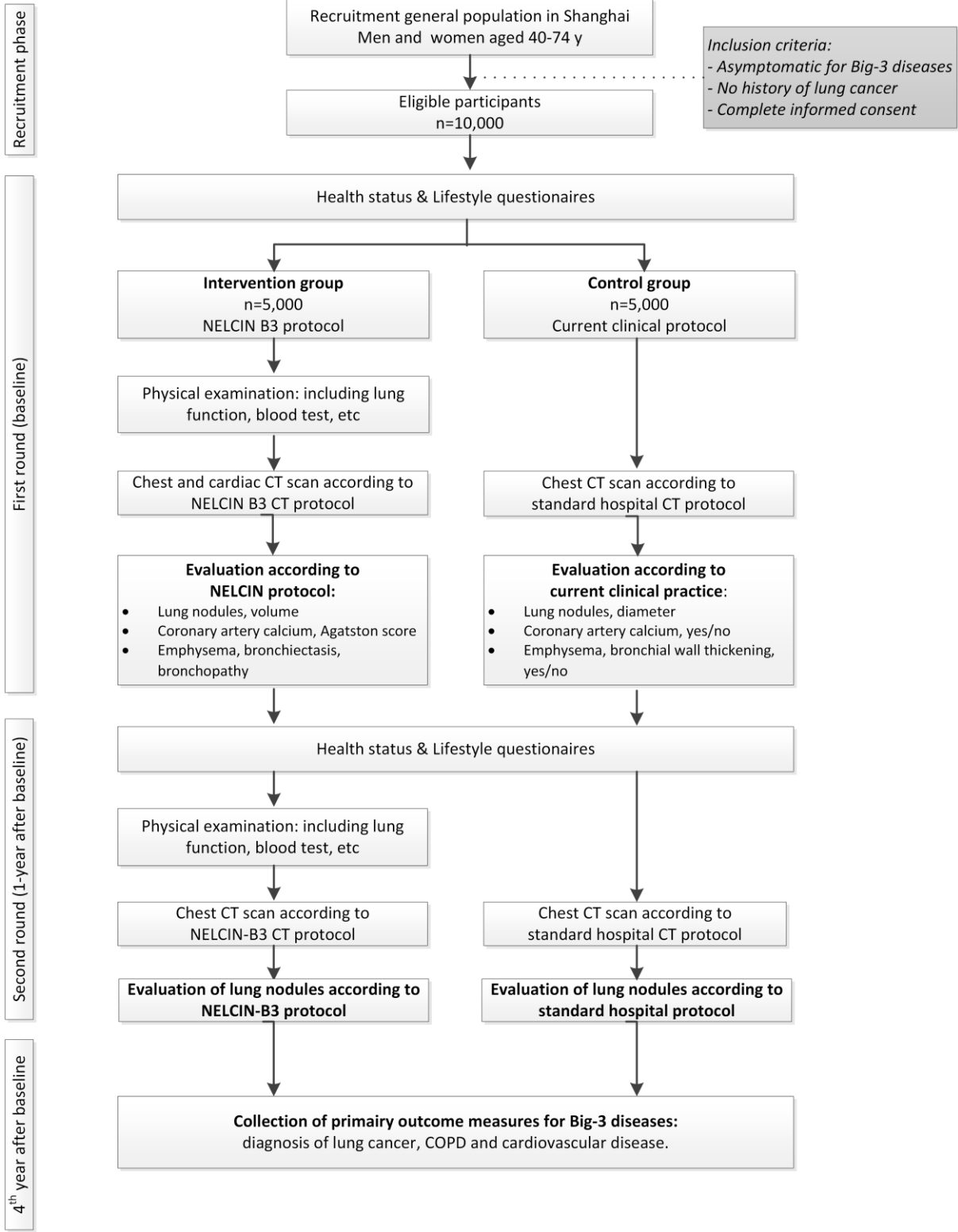


Figure 2. Baseline NELCIN-B3 lung nodules management protocol (for solid and part-solid nodules) in the intervention group, adapted from NELSON study⁹.

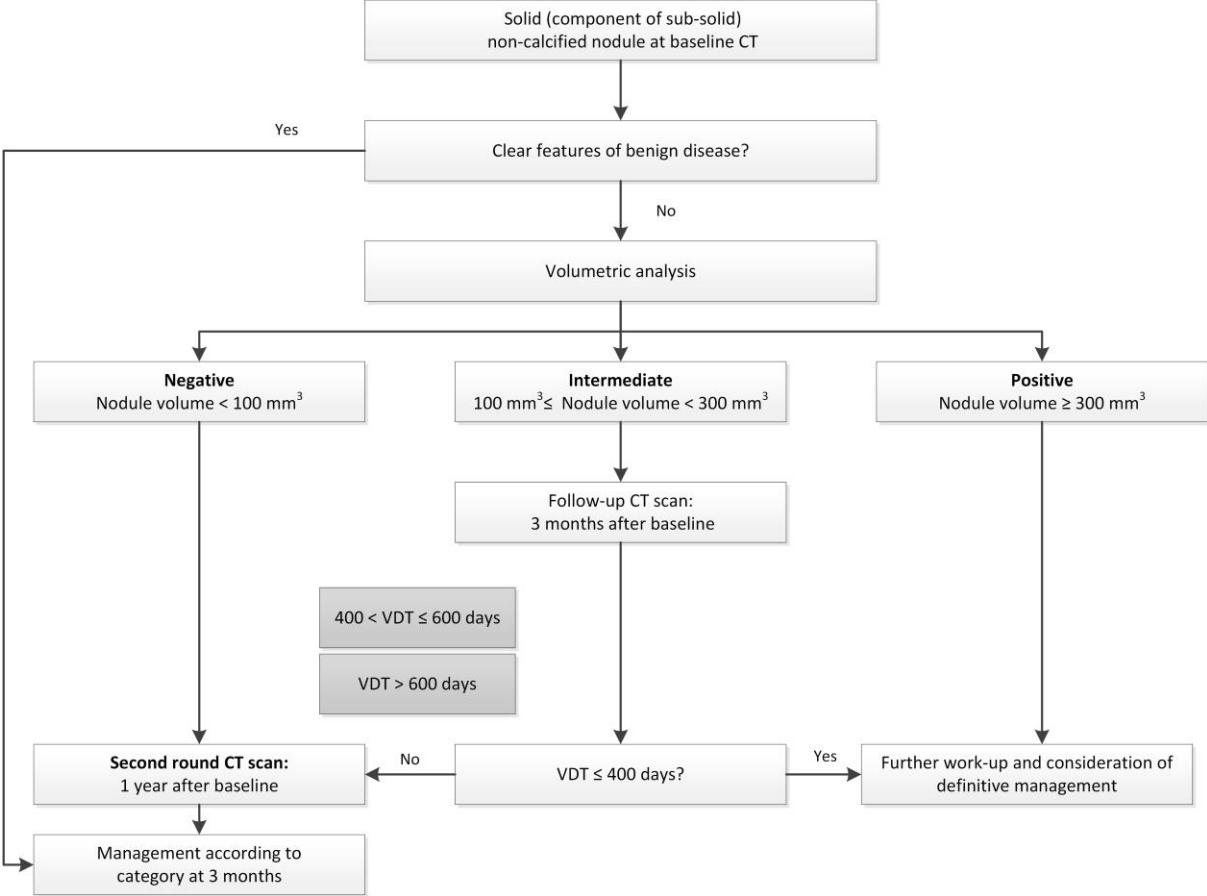
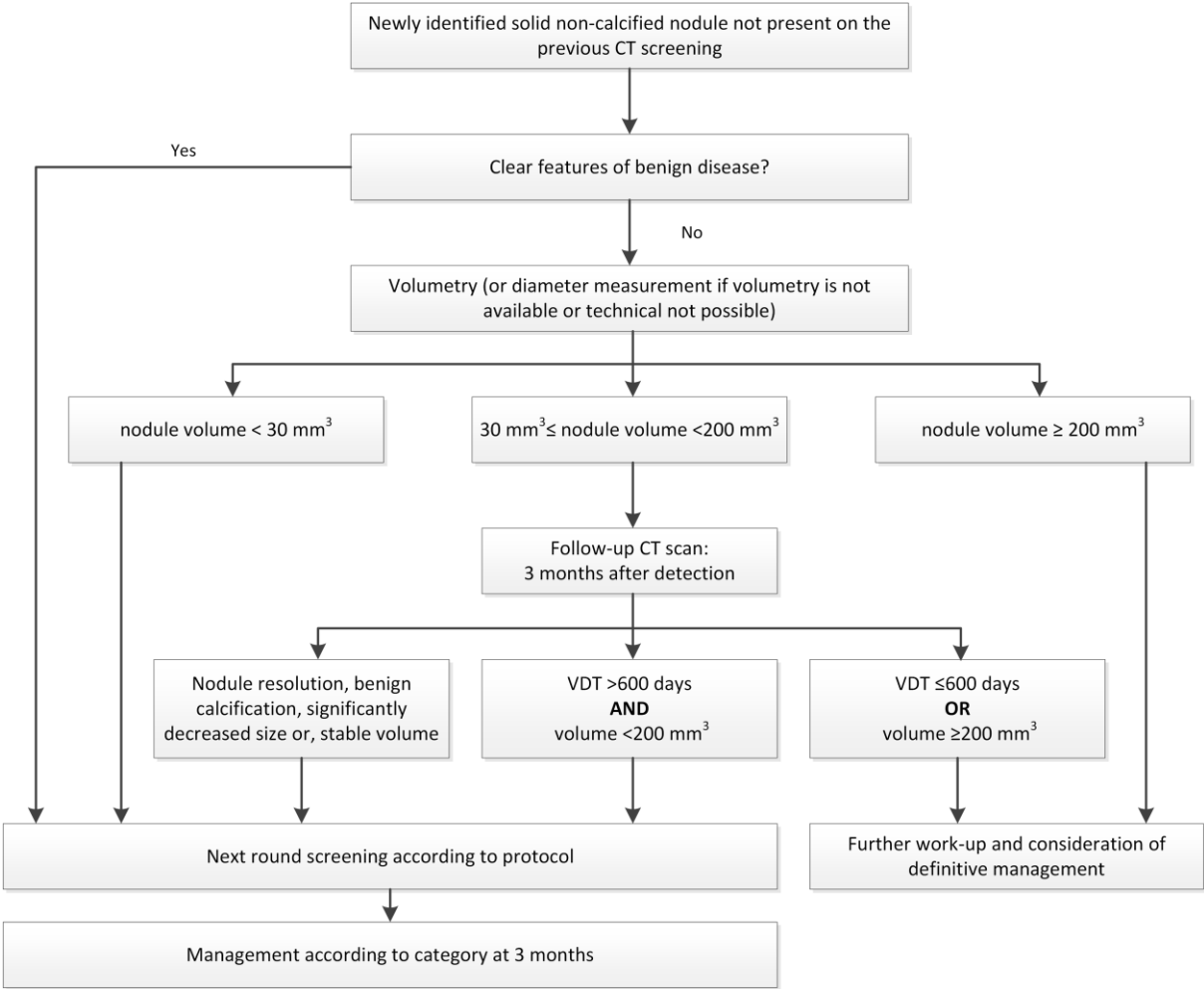


Figure 3. NELCIN-B3 screen detected incidental solid (component) nodules at follow-up in the intervention group, adapted from NELSON study ⁹.



Appendix

Table S1 The NELCIN-B3 scan parameters for chest and cardiac CT image acquisition in the intervention and control groups

Scan parameters	Intervention group			Control group
	Chest	Cardiac		Chest
		Weight <80 kg	Weight ≥80 kg	
<i>Scan mode</i>	Spiral, pitch 0.758	Sequential	Sequential	Spiral, pitch 0.98
<i>Tube voltage (kVp)</i>	120	120	120	120
<i>Tube current (mAs)</i>	19 (dose right index 3)	30	50	50
<i>Rotation time (ms)</i>	270	270		330
<i>Matrix</i>	512x512	512x512		512x512
<i>ECG triggering</i>	No triggering	65%	65%	No triggering
<i>Dose Modulation</i>	On (dose right index 3)	Dose right off	Dose right off	Dose right off
<i>Automated patient instruction</i>	Inspiratory breath-hold	Inspiratory breath-hold		Inspiratory breath-hold
<i>Direction</i>	Craniocaudal	Craniocaudal		Craniocaudal
<i>Upper limit</i>	Top of the lungs	Below carina	Below carina	Top of the lungs
<i>Lower limit</i>	Dorsal pleural sinus	Apex/ bottom edge heart	Apex/ bottom edge heart	Dorsal pleural sinus

Table S2 The NELCIN-B3 reconstruction parameters for chest and cardiac CT image acquisition in the intervention group

Reconstruction parameters	Chest				Cardiac	
	Recon 1	Recon 2	Recon 3	Recon 4	Recon 1	Recon 2
<i>Slice thickness (mm)</i>	1.0	1.0	1.0	1.0	3.0	3.0
<i>Slice increment (mm)</i>	0.7	0.7	0.7	0.7	1.5	1.5
<i>Field of view (mm)</i>	350 (400 in case thorax too large)	350 (400 in case thorax too large)	350 (400 in case thorax too large)	350 (400 in case thorax too large)	250	250
<i>Reconstruction kernel</i>	Sharp(C)	Detail(D)	Smooth(A)	Standard(B)	Smooth(A)	Standard(B)
<i>Reconstruction method</i>	FBP	FBP	FBP	FBP	FBP	FBP
<i>Window</i>	Lung	Lung	Mediastinum	Mediastinum	Mediastinum	Mediastinum