The protocol for the Prospective Urban Rural Epidemiology China Action on Spine and Hip status study

Kai Li, Yong Zhang, Ling Wang, Yang-Yang Du, Wei Tian, Hui Chen, Lu Yin, Jian Bo, Yang Wang, Wei Li, Li He, Wen-Hua Zhao, Shao-Qi Xu, Lin-Fen Zhao, Jun Zhou, Feng-Zhe Wang, Yu Liu, Lei Zhu, Yi-Zhong Chen, Xiao-Lin Zhang, Xiao-Guang Hao, Zhi-Wei Shi, Jun-Ying Wang, Ji-Man Shao, Zhi-Jian Chen, Ren-Sheng Lei, Gang Ning, Qian Zhao, Yong-Hong Jiang, Ya-Hong Zhi, Bao-Qing Li, Xiao Chen, Quan-Yong Xiang, Liang Wang, Yuan-Zheng Ma, Shi-Wei Liu, Xiao-Guang Cheng

1Department of Radiology; 2Department of Spine Surgery, Beijing Jishuitan Hospital, Beijing 100035, China; 3Medical Research & Biometrics Center, National Center for Cardiovascular Disease, Beijing 102500, China; 4National Institute for Nutrition and Health, Chinese Center for Disease Control and Prevention, Beijing 100050, China; 5Department of Radiology, Nanjing University of Chinese Medicine Affiliated Wujin Hospital of Traditional Chinese Medicine, Changzhou 213161, China; 6Department of Radiology, the 4th People's Hospital of Shenyang, Shenyang 110031, China; 7Department of Prevention and Healthcare, Shenyang No. 242 Hospital, Shenyang 110034, China; 8Department of Radiology, the People's Hospital of Dayi County, Chengdu 611330, China; 9Department of Prevention and Healthcare, Dayi County Public Health Hospital, Chengdu 611330, China; 10Department of Radiology, Taiyuan Central Hospital, Taiyuan 030009, China; 11Balingqiao Community Health Service Center, Taiyuan 030013, China; 12Department of Radiology, the Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, Nanchang 330006, China; 13Nanchang County Center for Disease Control & Prevention, Nanchang 330200, China; 14Department of Radiology, West China Second University Hospital of Sichuan University, Chengdu 610041, China; 15General Practice Department, West China Hospital of Sichuan University, Chengdu 610041, China; 16Department of Radiology, Xi'an Honghui Hospital, Xi'an 710054, China; 17Department of Prevention and Healthcare, Hospital of Xidian University, Xi'an 710071, China; 18Department of Radiology, Beijing Shijingshan Hospital, Beijing 100043, China; 19Department of Radiology, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, China; 20Jiangsu Provincial Center for Disease Control and Prevention, Nanjing 210019, China; 21Center of Orthopedics, the 309th Hospital of People's Liberation Army, Beijing 100091, China; 22National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 100050, China

Correspondence to: Prof. Xiao-Guang Cheng. Department of Radiology, Beijing Jishuitan Hospital, East Xujiekou Street, No.31, Xicheng District, Beijing 100035, China. Email: xiao65@263.net.

Abstract: The Prospective Urban Rural Epidemiology (PURE) China Action on Spine and Hip status (CASH) study focused on the prevalence of osteoporosis and spinal fracture in China. The aim of the PURE CASH study is to determine the prevalence of osteoporosis and spinal fracture, and explore the potential relationship between spinal fracture and bone mineral density (BMD). This study is a prospective large-scale population study with a community-based sampling and recruitment strategy. The aim is to determine the prevalence of osteoporosis and vertebral fracture in this population, to evaluate the association between vertebral fractures and BMD values, and to assess the prediction power of BMD for incident fractures. Participants in the PURE CASH study are all from the PURE study in China, recruited from 12 centers in 7 Chinese provinces. The inclusion criteria are that participants should be aged more than 40 years and able to give informed consent. Exclusion criteria are pregnant women, individuals with metal implants in the lumbar spine, use of medications or the existence of any disease or condition known to have a major influence on BMD, and inability to give informed consent. A total of 3,457 participants undergo a quantitative computed tomography (QCT) scan of the upper abdomen. The scanning parameters are as follows: 120 kVp at all centers, mAs between 75 and 200, FOV 40 cmx40 cm. The BMD values of L1 to L3 are measured, and the average BMD calculated. The American College of Radiology QCT criteria for the diagnosis of osteoporosis is applied to determine the presence of osteoporosis. The scout view images of T4–L4 vertebrae are reviewed by two experienced radiologists for semi-quantification of vertebral fractures according to Genant's method.
Introduction

Osteoporosis is a systematic skeletal disorder characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in the fragility of bone and susceptibility to fracture (1). Osteoporotic fractures occur most commonly at the spine, hip, forearm and other sites, while hip fracture is associated with high mortality and morbidity (2,3). Studies have indicated an increasing incidence of hip fracture in Chinese cities (4,5), and this is a significant burden for society. Accurate and reliable knowledge of the prevalence of osteoporosis and osteoporotic fracture throughout China will be critical for policy-making and healthcare planning. A cross-sectional and population-based study conducted in Shanghai in 2010 showed that the prevalence of osteoporotic fractures was 14.9% in females (57.6±9.5 years) and 12.2% in males (58.5±10.1 years) (6). Results of Mister Osteoporosis Study and Miss Osteoporosis Study from 2001 to 2003 suggested that the prevalence of vertebral fractures (defined as grade ≥2 vertebral deformity according to Genant’s criteria) in Hong Kong was 5.0% among elderly men (mean age: 72.4 years old) and 12.1% among elderly women (mean age: 72.6 years old) (7).

In the past, dual energy X-ray absorptiometry (DXA) has been widely used to study the epidemiology of osteoporosis, and in the diagnosis and management of osteoporosis. It was demonstrated using DXA that the bone mineral density (BMD) of 85-year-old women reflected a loss of 32% at the spine and 30–35% at the femur measurement sites in China (8). The two-dimensional projection nature of DXA images makes the measurement susceptible to degenerative changes in the spine and aortic calcification. Our previous study verified that a substantial number of patients with osteoporosis were missed by DXA measurements (9). Quantitative computed tomography (QCT) is technically superior to DXA for measuring BMD in the spine and hip, and has attracted increasing attention in recent years (10-17). The diagnosis of osteoporosis by DXA relies on T score measurements at the spine and hip, and the calculation of T scores relies on the use of reference databases provided by the manufacturers. Therefore, the variations in the prevalence of osteoporosis reported in different studies may be partially due to the differences in the reference databases, and not indicative of true differences in the prevalence of osteoporosis. A diagnostic criterion of osteoporosis by QCT of a spinal trabecular volumetric BMD (vBMD) less than 80 mg/cm³ was recommended by the International Society for Clinical Densitometry in 2007 (17) and American College of Radiology in 2008 (18). Because the lateral scout view image of the CT scan can be used to assess for prevalent vertebral fractures (19-21), and vBMD measurements can be achieved simultaneously, QCT can provide accurate data on the prevalence of osteoporosis. However, the prevalence of osteoporosis and vertebral fractures using QCT data has not yet been studied in a Chinese population.

The Prospective Urban Rural Epidemiology (PURE) study is an international, large, multi-center, community-based, epidemiological cohort study in 18 countries, including China. The details of this study and the baseline characteristics have been reported (22,23). The details of Chinese participants and their baseline characteristics were reported recently by Peng et al. (24). The PURE China Action on Spine and Hip status (CASH) study focused on the prevalence of osteoporosis and osteoporotic spinal fractures in China. The participants in the PURE CASH study are all from the PURE study in China. The objectives of this study are: (I) to determine the prevalence of osteoporosis in this population by QCT vBMD measurement; (II) to determine the prevalence of osteoporotic vertebral fractures and their association with vBMD; (III) to determine the power of vBMD to predict future fractures in a follow-up study.

Study design

The PURE CASH study (identifier: NCT01758770) is a prospective, multicenter, epidemiological study. The subjects of PURE CASH study are enrolled from 12 centers (Beijing Jishuitan Hospital, Beijing Shijingshan Hospital, Taiyuan Central Hospital, West China Second University,...
Hospital of Sichuan University, Chengdu Second People’s Hospital, the People’s Hospital of Dayi County, the 4th People’s Hospital of Shenyang, Wujin Hospital of Traditional Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, the Second Affiliated Hospital of Nanjing University of Chinese Medicine, Xi’an Honghui Hospital, the Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine. From June 2013 to March 2017, all the subjects underwent QCT scans of the lumbar spine with thoracic and lumbar spine CT scout views. The participants of PURE CASH study will be followed up for incident fractures as required by the protocol of PURE study in the future.

Ethical approval is obtained from the ethics committee of the Beijing Jishuitan Hospital, Peking University (Approval No. 201210-01 and No. 201512-02). The study is conducted in accordance with ethical principles according to the Declaration of Helsinki and is consistent with Good Clinical Practice. Radiation safety and protection measures are strictly implemented in the whole study. Informed consent is obtained from every participant in the study.

The participants are from 12 centers in 7 Chinese provinces including Beijing, Liaoning, Shanxi, Shaanxi, Sichuan, Jiangsu and Jiangxi. The inclusion criteria are that participants should be aged over 40 years old and able to give informed consent. Exclusion criteria are pregnant women, individuals with metal implants in the lumbar spine, use of medications or the existence of any disease or condition known to have a major influence on BMD, and inability to give informed consent.

The estimation of sample size and the recruitment

When enrollment commenced the estimated number of participants is more than 3,000. Since there is no population based QCT prevalence data available in China, we use the published DXA data for osteoporosis prevalence in China instead. The prevalence of osteoporosis by DXA BMD measurements is between 5% and 20% according to areal measurements (25). Under a two-sided 0.05 alpha level, 500 participants per center is sufficient to ensure a ±3.5% estimated precision on the osteoporosis rate for each area (the width of the 95% confidence interval will be less than 7.0%). Since QCT is more sensitive than DXA for detecting osteoporosis (9), the detected prevalence of osteoporosis is expected to be higher. Hence the current sample size is sufficient to ensure adequate accuracy.

The BMD measurement of vertebral body

The vBMD values (mg/cm$^3$) of the L1, L2 and L3 vertebral body are measured according to the Mindways protocol. The average vBMD value of L1–L3 is calculated as the spinal vBMD outcome of each subject.

The diagnosis of osteoporosis

The diagnostic criteria of osteoporosis for QCT, recommended by the International Society for Clinical
Densitometry in 2007 (17) and American College of Radiology in 2008 (18), is used to classify the subjects as normal if average vBMD >120 mg/cm$^3$, osteopenia if vBMD between 120 and 80 mg/cm$^3$, and osteoporosis if vBMD <80 mg/cm$^3$.

The vertebral fracture assessment (VFA)

The lateral scout view images from the QCT scans are used to detect vertebral body fractures according to Genant’s semiquantitative method (27,28). Each vertebral body is classified as normal (grade 0), mild (grade 1, approximately 20–25% depression in height and a reduction in area 10–20%), moderate (grade 2, approximately 25–40% depression in height and a reduction in area 20–40%), or severe (grade 3, more than 40% reduction in height and area) fracture (27,28). The digital images are displayed and viewed on a professional work station with the RadiAnt DICOM Viewer software (Version 4.5.9, Medixant Company, Poland); the quantitative diagnosis is performed by two musculoskeletal radiologists with many years’ experience of vertebral fracture assessment. The outcomes are determined via consensus opinion. A subject is considered to have a spinal osteoporotic fracture if any one of the T4–L4 vertebral bodies had a VFA score ≥ grade 1. The highest VFA score for each subject will be considered the severity.

The benefit for the study participants

The vBMD results along with any abnormal CT scan findings will be provided to the participants.
Conclusions
This study is the first to determine the prevalence of osteoporosis and vertebral fractures in China by QCT measurements in a large-scale, multicenter population. Accurate data on the prevalence of osteoporosis and osteoporotic fracture in China can be obtained, and their association can be assessed. These data may have great significance for future policy-making and the prevention of osteoporosis and osteoporotic fractures in China.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: Ethical approval was obtained from the ethics committee of the Beijing Jishuitan Hospital, Peking University (Approval No. 201210-01 and No. 201512-02) and informed consent was obtained from every participant in the study.

References

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Questionnaire of PURE CASH Study

PURE Identifier: ____________________

Name: _______ Gender: _______ Date of Birth: _______ (mm)/ _______ (dd)/ _______ (yy)

Age: _______ years old  Nation: _______

Weight: _______ kg  Height: _______ cm

Waist Circumference: _______ cm  Hip Circumference: _______ cm

Blood Pressure: _______ (SBP)/ _______ (DBP) mmHg

Fasting blood-glucose: _______ mmol/L

Age of menopause (if postmenopausal females): _______ years old

Fracture History: None _______

Yes _______ Date of Fracture if any _______ Fracture Site if any _______

Hip Fracture History of parents: None _______ Yes _______

Tobacco Use: No _______ Yes _______ How many cigarettes per day if any _______

Glucocorticoids use: No _______ Yes _______

History of Rheumatic Arthritis: No _______ Yes _______

History of Secondary Osteoporosis: No _______ Yes _______

[NOTE: Secondary osteoporosis referred to the osteoporosis caused by Type I diabetes mellitus (insulin-dependent diabetes mellitus), adult osteogenesis imperfecta (idiopathic osteopsathyrosis), hyperparathyroidism, hypogonadism or premature menopause (age <45 years old), chronic malnutrition or malabsorption, and chronic hepatopathy.]

Alcohol Use Amount equal to or more than 3 Units per day: No _______ Yes _______

[NOTE: One unit means 285 mL beer, 30 mL spirit, 120 mL wine, 60 mL fruit wine, or 60 mL sake.]

Date: _______ (mm)/ _______ (dd)/ _______ (yy)

Signature: _______