BMJ Open

The Qingdao Port Cardiovascular Health Study: Design and Rationale of a Prospective Longitudinal Cohort Study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-008403
Article Type:	Protocol
Date Submitted by the Author:	04-Apr-2015
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Primary Subject Heading:	Cardiovascular medicine

Secondary Subject Heading:	Epidemiology
Keywords:	population surveillance, cardiovascular diseases, longitudinal studies, cohort studies, outcomes research

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Key Words: population surveillance; cardiovascular diseases; longitudinal studies; cohort studies; outcomes research

Word Count: 3,367

ABSTRACT

Introduction In China, efforts are underway to respond to rapidly increasing rates of heart disease and stroke. Yet the epidemiology of cardiovascular disease in China may be different from that of other populations, with implications for intervention and prognosis; however, much remains unknown. There is a critical need for population-based studies that provide insight into the risk factors, incidence, and outcomes of cardiovascular disease in China.

Methods and analysis The Qingdao Port Cardiovascular Health Study is a population-based prospective, longitudinal cohort study of employees of the Qingdao Port Group in China that is designed to investigate the burden of cardiovascular disease and the socio-demographic, biological, environmental and clinical risk factors associated with disease onset and outcomes. Since 2000, nearly all employees volunteer for participation in the Study, which is governed by extensive quality control mechanisms. Trained medical personnel perform annual health examinations. Measurements include a questionnaire (capturing demographic and employment information, medical history, medication use, health behaviors and health outcomes), physical examination, electrocardiography, blood and urine analysis, echocardiogram and carotid ultrasound. Additional non-cardiovascular assessments include a baseline chest X-ray, abdominal and thyroid ultrasound, as well as breast and uterine ultrasound for women. Cardiovascular outcomes are assessed through self-report, and more recently, also via medical insurance claims data and hospital medical records. In 2013, the Study established a bio-repository for future genetic and proteomic analyses.

Ethics and dissemination The ethics committees of the Qingdao Fuwai Hospital, which is responsible for collecting the data, approved the study. Yale University, a collaborator, approved the analysis of

data. Knowledge generated will be disseminated in the peer-reviewed literature, and will inform population-based strategies to improve cardiovascular health in China.

Trial registration number NCT02329886

Strengths and limitations of this study:

- This is a prospective cohort study has been conducted for above 10 years.
- The study collected a variety of information including health-related risk factors, clinical outcomes and bio-samples, allowing a wide ranging assessment of risk factors and genetic factors related to cardiovascular disease onset and cardiovascular outcomes.
- Findings will have broad implications for China's workforce and for employer-based healthcare.
- Participants are limited to a single company and may not be representative of the larger population of China.

INTRODUCTION

Epidemiologic studies are the cornerstone for understanding cardiovascular risk factors and disease. Decades of research extending from the Framingham Heart Study and other cardiovascular studies (e.g., Atherosclerosis Risk in Communities Study) provide insight into the complex interplay between biology, behavior, environment, and genes on the risk of cardiovascular disease and stroke.[1-4] However, existing studies of the epidemiology of cardiovascular disease may have limited relevance to other populations, particularly in countries with different health behaviors and environments.

The relationships between risk factors and cardiovascular disease outcomes differ between populations. As demonstrated in the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, along with other studies, metabolic, dietary and other lifestyle factors do not consistently portend the same cardiovascular risk across populations.[5-11] The graded relationship between higher cholesterol levels and mortality from coronary heart disease varies among Western countries[12] and may differ in China.[13 14] Studies also demonstrate differences in the epidemiology of stroke, with the slope of the relationship between blood pressure and stroke steeper among Asian populations as compared with Australian populations,[15] and hemorrhagic stroke occurring more frequently in Chinese populations than in Western populations.[16] In summary, the epidemiology of heart disease and stroke in China, and its associated risk factors, may be different from that of other populations, and thus may have different implications for intervention and prognosis. Understanding potential differences in the epidemiology and outcomes of cardiovascular disease in China requires population-based studies.

Well-conducted, population-based longitudinal studies focused on cardiovascular disease are critical, especially as China is experiencing remarkable changes in the cardiovascular risk of its population.[17-20] Similar to other developing countries undergoing an epidemiologic transition, there has been a dramatic rise in the prevalence of non-communicable diseases such as cardiovascular disease and cancer.[13 21] Approximately 1 in 5 Chinese adults (~230 million people) have cardiovascular disease, the prevalence of which is expected to double in the next decade.[22] In 2010, 11% of the Chinese population was estimated to have diabetes, up from 1% in 1980; Chinese individuals now account for one-third of all cases of diabetes worldwide.[23] Beyond the expected rise in cardiovascular disease associated with longer life expectancy,[24] other factors such as urbanization,[25] environmental pollutants,[26-28] and sociocultural shifts[29] have been associated with the increasing prevalence of obesity,[30] hypertension,[31] diabetes,[32] and smoking,[33] though these relationships with cardiovascular disease have not been well described in China.[34 35]To date, there are few contemporary, longitudinal, population-based studies to identify factors associated with heart disease and stroke in the Chinese population.[36 37]

Accordingly, the Qingdao Port Group and its affiliated hospital, Qingdao Fuwai Hospital, established the Qingdao Port Cardiovascular Health Study in 2000, a prospective, longitudinal cohort study of employees of the Group, with the aims of monitoring the incidence of cardiovascular disease and associated risk factors, and more recently, of other non-communicable diseases. Knowledge gained from this study will be used to guide China's efforts in preventing and managing heart disease and stroke. In this paper we describe the design and investigational priorities of the Qingdao Port Cardiovascular Health Study.

METHODS

Setting and recruitment

The Qingdao Port Group of the Shandong province in China is one of the oldest and largest shipping and trade companies in the world. (Figure 1) The workforce is diverse, with administrative personnel, technical personnel (e.g., pilots, computer analysts and information technology specialists, police, teachers, physicians, nurses and other hospitals staff), production operators, ship workers, dockworkers, and drivers. Among them, ship-and dock-workers account for the majority of all staff.

The company contributes to each employees' health insurance plan, which is administered by the Qingdao medical insurance bureau. The plan covers annual health assessments, on-site ambulatory medical care, and coverage of inpatient services rendered at the Qingdao Fuwai Hospital, the local hospital and partner in this study, as well as other public hospitals in Qingdao city. Most, though not all, employees participate in the annual health screening. Migrant workers are not covered by the local health insurance and do not receive annual health examinations, effectively excluding them from Study participation.

All employees who present for an annual health assessment are eligible for Study participation and receive information about the Study. Prior to 2013, employees were verbally asked to participate. Since then, however, employees sign an informed consent document prior to enrollment. (Appendix 1: Translated informed consent document). Among the employees who present for a health assessment, almost all (98%) agree to participate in the Study. At each annual visit, employees renew their agreement to participate. Participants are informed that the data are confidential.

The annual health assessments, offered at the three work sites, serve as the platform for data collection. The organizational structure for the study is presented in Figure 2.

Study design and investigational priorities

The Qingdao Port Cardiovascular Health Study was started in 2000. The study was initially intended to monitor cardiovascular disease trends and to understand risk factors contributing to chronic conditions with a focus on heart disease and stroke.[38 39] In 2012, the Qingdao Port Group partnered with the Fuwai Hospital in Beijing, China's National Center for Cardiovascular Diseases (NCCD), resulting in the expansion of data collected, including biological samples for genomics research, and revisions to the questionnaire to capture non-cardiovascular outcomes, including cancer, liver disease and other prevalent conditions in China.[13 40 41] In addition, in 2013, the Study began linking health assessment data with medical claims and hospital medical records to strengthen the Study's capacity to assess health outcomes.

The collaboration also helped to fortify several investigational priorities: 1. Surveillance of cardiovascular disease (and more recently, other non-communicable diseases), and cardiovascular risk factors, health outcomes and trends; 2. Investigation of socio-cultural, biological, behavioral, social, and environmental factors on work productivity, cardiovascular disease onset and cardiovascular health outcomes; 3. Development and validation of risk models to predict cardiovascular events; 4. Implementation and assessment of health behavior monitoring; and 5. Genetic and proteomic analysis of biological samples to elucidate disease mechanisms and inherited risk profiles.

Cohort

From 2000 through 2013, a total of 32,404 study participants contributed 221,923 health assessments. In this cohort, the mean age is 43.4 (SD 12.9) and 79% were male, consistent with the demographics of the company. Participants ranged in occupation: loading/unloading (9.7%); warehouse clerk (8.0%); ship crew (18.8%); other shipping and dock-workers (29.9%); management (19.9%); other (13.7%). Table 1 describes trends in participants' characteristics across three time-periods: 2000, 2005 and 2010.

Table 1. Trends in Characteristics of Study Participants (2000 to 2010)

Description	2000		2005		2010	
	#	%	#	%	#	%
TotalParticipants	12023		14152		16378	
Retirees	NA	NA	3369	23.8	4594	28.1
Demographics						
Age(Mean;SD)	39	8.7	45	12.0	45	13.7
Gender						
Male	9227	76.7	10945	77.3	13076	79.8
Female	2796	23.3	3207	22.7	3302	20.2
CardiovascularProfile						
HighBloodPressure*						
Yes	3176	26.4	5457	38.6	6451	39.4
Diabetes†						
Yes	396	3.3	838	5.9	1458	8.9
Hyperlipidemia‡						
Yes	600	5.0	1749	12.4	5499	33.6‡
AcuteMyocardialInfarction						
Yes	NA	NA	66	0.5	128	0.8
Stroke						
Yes	66	0.5	130	0.9	188	1.1
Anthropometrics						
Waist(cm)						
Mean(SD)	81.6	11.2	83.9	9.6	86.6	12.3
BMIcm/kg2§						
Normalbodyweight(<24)	5852	48.7	5317	37.6	6313	38.6
Overweight(24to<28)	4456	37.1	5972	42.2	6831	41.7
Obese(>=28)	1690	14.1	2586	18.3	3044	18.6
SystolicBloodPressure						

Mean(SD)	121	17.1	122	18.3	125	20.9
DiastolicBloodPressure						
Mean(SD)	80	12.1	82	11.6	82	11.2

*Self-report or mean blood pressure >=140 systolic or >=90 mmHg diastolic or antihypertensive medication therapy
†Self-report or fasting glucose >=7.0 mmol/L or glucose lowering medication
‡Self-report or lipid lowering therapy for year 2000; self-report only for year 2005; self-report or dyslipidemia (either: total cholesterol ≥5.2mmol/L or low-density lipoprotein ≥3.4 mmol/L or high-density lipoprotein <1.0 mmol/L or triglycerides ≥1.7 mmol/L) or lipid lowering medication therapy for year 2010

Health assessment components

Annual health assessments, which are performed by 35 trained physicians and nurses, consist of a questionnaire, physical examination, electrocardiography, laboratory testing, and bio-sampling, along with cardiac and non-cardiac imaging that varied during different years of the study. Currently, there are 466 unique variables summarized by domain in Appendix 2.

1. Questionnaire

A standardized questionnaire is administered by trained personnel during a face-to-face annual health assessment. Questions are adapted from prior epidemiologic studies,[42] and when available, questionnaires validated in Chinese are used.[43] The following domains are assessed: demographics (e.g., income, education, family structure); personal medical history (e.g., medical history, medication use and adherence); family history; health behaviors (e.g., nutritional intake; physical activity;[44] smoking; alcohol use/abuse – assessed using the Alcohol Use Disorders Identification Tool [AUDIT][43]); health care utilization (e.g., hospitalizations; use of traditional Chinese medicine); menopause (including hormone use); emotional health (e.g., anxiety, stress); and employment structure (e.g., physical labor; shift-work).

2. Physical examination

A detailed, comprehensive physical examination is conducted at baseline by trained medical staff. Nurses measure height, weight, waist circumference, hip circumference, blood pressure, and heart rate. Physicians perform a detailed eye and ear exam, dental assessment, thyroid palpation, cardiopulmonary auscultation, and abdominal examination. Nurses and physicians follow standardized protocols for measurement and examination. Height (cm), weight (kg), and waste and hip circumference are measured using sonographic technology (Ultrasound Height & Weight Machine, TCS-160D-W/H, Shenzhen Sonka Electronic Techology Co.,Ltd, Guangdong, China), averaged to the nearest 0.1 unit. Instruments are calibrated weekly with phantom mannequins. Blood pressure and heart rate are measured after the patient has been seated for 5 minutes using a calibrated electronic sphygmomanometer. Blood pressure of the dominant arm is performed by placing the cuff at heart level and taking the average of three measurements spaced 1 minute apart. Heart rate is recorded contemporaneously with each blood pressure measurement.

3. Laboratory tests

Venipuncture, performed by trained nurses, is obtained annually. Some blood chemistries are repeated each year (e.g., fasting glucose, lipid profile, creatinine). Tests performed intermittently include: liver function, thyroid function, and biomarkers (e.g., tumor specific growth factor).

4. Bio-samples for future analysis

Since 2013, participants are invited to submit bio-samples, including blood, urine and saliva samples, for storage and future DNA, RNA and biochemical analysis. Over 90% of Study participants have consented to date. Whole blood samples are drawn into EDTA, serum gel, heparin lithium, and Tempus

blood RNA tubes (Applied Biosystems, Foster City, California, USA) for future gene expression analysis. When stored in Tempus tubes at −80°C, the whole blood RNA retains high integrity and purity for over a six year period.[45] To collect saliva, participants are asked to chew a cotton roll for 45 seconds; the cotton roll is placed into a Salivette® tube (Sarstedt AG & Co, Nümbrecht, Germany). Within 24hours, trained nurses centrifuge blood and saliva samples and divide and transfer the samples into cryovials, according to standard protocols. Urine is transferred directly into cryovials. All samples are immediately stored at -80℃, and are transported to Fuwai Hospital, NCCD for long-term storage within two months.

5. Additional testing

Electrocardiography is performed every year. Additionally, specific screening tests were conducted during different years including: chest x-ray, echocardiogram, carotid ultrasound, abdominal ultrasound (including liver, gallbladder and kidney), thyroid ultrasound, and breast and uterus ultrasound. All imaging tests are conducted by certified technologists in accordance with standards set forth by the Ministry of Health.

Follow-up

Follow-up health assessments are performed annually. Among 32,404 study participants from 2000-2013, more than half (18,111; 55.9%) have 5 or more years of follow-up; 11,537 (35.6%) participants have 10 or more years of follow-up. (Figure 3) The components of the follow-up visit are the same as the baseline assessment and include a face-to-face interview, physical examination, laboratory testing and imaging exams specified for that year. New participants are recruited each year (Figure 4) and, since 2003, participants are followed into retirement, up until death. In China, the statutory retirement

age for general workers is 60 years for men and 50-55 years for women, depending on their job position. Among heavy laborers, the retirement age is 55 years for men and 45 years for women. Senior professionals may work until the age of 65-70 years. Since 2003, retirees account for approximately one-quarter of all annual health assessments each year, with approximately 7,000 retirees in the study.

Outcomes

The following cardiovascular outcomes are collected: unstable angina; acute myocardial infarction; revascularization with either percutaneous coronary intervention or coronary artery bypass grafting; heart failure; stroke; and all-cause death. Outcomes are collected by self-report, and more recently, using Qingdao medical insurance bureau claims data. As part of the annual health questionnaire, participants are asked to report information on newly diagnosed diseases, hospitalizations, and treatments that occurred in the previous year. Self-reported health outcomes that were elicited prior to 2013 are actively being linked with medical claims data. Prospectively, since 2013, medical claims are linked with health assessment data every 3 months, independent of whether participants self-reported a clinical outcome. From the medical claims, the following information is abstracted: admission date, discharge date, discharge diagnoses and corresponding International Classification of Disease (ICD) codes; and discharge status. Death information is collected from death certificates, medical records from hospitalizations, autopsy reports and interviews with relatives and physicians.

A subset of outcomes is adjudicated through the collection of medical records of participants who self-report a new disease or clinical event. In 2013, 855 participants reported hospitalizations; of these, complete medical records were obtained for the 300 participants hospitalized at Qingdao Fuwai

Hospital. Among patients hospitalized outside of Qingdao Fuwai Hospital, medical records from 246 participants were obtained. These records came directly from participants, though there are efforts to develop a process that will enable the direct collection of Study participants' medical records from outside hospitals. Consistent with other cardiovascular research protocols,[46] adjudicators review the clinical diagnosis and the claims-based ICD code. Discrepancies between the medical record and claims data are resolved by the research guidance committee in Fuwai Hospital, NCCD.

Quality assurance and control

All research personnel are trained in conducting face-to-face interviews, blood pressure measurements, anthropometry, blood collection and sample processing, electrocardiography and data entry. Each year, all equipments, including the biochemical analyzer, ultrasound machine, x ray machine, electronic sphygmomanometerand ultrasound stadiometer are tested and calibrated by the Qingdao Institute of Measurement and Testing and the Qingdao Institute of Weighing Apparatus Management; annual calibration certificates by these two institutes are required. The validity of all measurements are checked monthly by examination of data outliers and missing fields. Additionally, site monitoring is conducted by two trained research staff from Fuwai Hospital, NCCD every 3-6 months, assessing: (1) the completeness of the documentation and (2) fidelity to protocol for recruitment, health screening, physical examination and sample collection and processing. Finally, annual meetings are held to discuss problems with measurement and data entry and to optimize study processes.

Data are collected at the three sites by trained physicians and nurses. From 2000-2012, data were collected on paper and double-entered by two different researchers into a computer-based system to reduce error. Since 2013, results from the questionnaire, physical examination, laboratory testing and

other examinations are collected electronically with an Internet-based data management system developed specifically for the study. To increase the validity and reliability of the data, this system included predefined data formats, predetermined data ranges for quantitative data, and required fields. After research personnel enter the data, internal data checks are performed to confirm that the data are correctly entered. Finally, prior to the beginning of each measurement year, all personal information is verified (name, sex, ID number, work ID, company, department, contact telephone number and address); these steps improve the accuracy of participants' information, decrease the duration of face-to face interview time and facilitate linkage with medical insurance records.

Data security and management

All data are treated as protected health information and are securely stored in an encrypted and password-protected database. Laptops are password-protected, and all research personnel have individual passwords to log-in to the system. All data between the three sites are independent, which means research personnel only have access to the data collected at their own site.

All source data, including questionnaires, health assessment results, hospitalization and clinical medical records, are securely stored in the 3 clinic sites of the Qingdao Fuwai Hospital. The electronic version of the files as well as the image files of electrocardiograms and chest x-rays are securely stored on the servers of Qingdao Fuwai Hospital. The Research Guidance Committee, comprised of investigators from the Fuwai Hospital, NCCD and the Qingdao Fuwai Hospital, make the ultimate decisions on the usage of the data governed by institutional review board approval.

ETHICS AND DISSEMINATION

The ethics committees of the Qingdao Fuwai Hospital, the Fuwai Hospital, NCCD, and Yale University approved the study. Since 2013, written informed consent is obtained from all participants upon entry into the study. In the informed consent it is stated that all personal information and results of the health examination, laboratory tests and other studies are confidential and stored in an encrypted database. Knowledge generated from this study will be disseminated in the peer-reviewed literature, and will inform population-based strategies to improve the cardiovascular health of employees of the Qingdao Port Group and of China, at large.

The unprecedented rise in the incidence of cardiovascular disease in China has prompted efforts to better understand the etiology of heart disease and stroke, including factors mediating health outcomes. Important to this challenge are longitudinal, epidemiologic studies, of stable populations. The Framingham Heart Study is perhaps the most recognized and influential existing population study,[1] resulting in over 15,000 publications since its inception in 1948. However, there are limitations in translating observations and findings to more diverse, non-Caucasian populations. The Multi-Ethnic Surveillance of Atherosclerosis (MESA) and Jackson Heart Study[47] are two examples of population-based studies, predominantly adults of African and Latino origin that reflect the need for a more nuanced understanding of cardiovascular disease among diverse populations. Similarly, the complex interplay between genes, biology, behavior, and environment, may be very different in an Asian population of Chinese adults, thereby warranting more specific epidemiologic investigation.

The Qingdao Port Cardiovascular Health Study is uniquely positioned to measure disease incidence and trends, characterize the complex relationships between biology, environment, culture, and behavior with disease onset, trajectories and outcomes, and ultimately inform the approach to cardiovascular

disease prevention and population health, especially among China's urban, working population. In this Study population, comparison of cardiovascular risk factors across three time periods (2000 to 2005 to 2010) demonstrates an increased prevalence of hypertension (26.4% to 38.6% to 39.4%) and diabetes (3.3% to 5.9% to 8.9%). The 2005 estimates for hypertension and diabetes are similar to those observed in the 2005 International Collaborative Study of Cardiovascular Disease in Asia (InterAsia).[48]Other Chinese population-based studies, such as the China National Diabetes and Metabolic Disorders Study (2007–2008), while nationally representative, are cross-sectional and less comprehensive.[18 49]The Singapore Chinese Health Study[50] and the Chinese Health and Retirement Longitudinal Study (CHARLS)[51]provide data on older populations, though they are not focused on cardiovascular disease and have limited follow-up data. To date, there are no longitudinal, population-based cardiovascular studies of the urban, working population of China.

Knowledge generated from the population of the Qingdao Port Cardiovascular Health Study will have broad implications for China's workforce and for employer-based healthcare, wherein large employers contract with health systems to provide comprehensive health care services to its employees, including health screenings, outpatient medical care and inpatient services. In 2006, approximately 160 million people (about 28% of the urban population) were covered by employer-based health insurance.[52] This Study, which aligns research objectives with current health challenges, is embedded in the employer-based health services model, and can thereby foster knowledge dissemination and translation among such employers. Importantly, the rigorous methodological design and health data collection, follow-up into retirement, and linkage of health screening data with insurance claims and medical records, will provide a rich opportunity to investigate disease trajectories and outcomes and inform approaches to population-based healthcare delivery. The Study is supported by the Fuwai Hospital, NCCD– a clinical

research group with longstanding expertise in standardized data abstraction, cataloguing, and linkage, ensuring excellent quality control and organization for scientific investigation.[53-55]

There are some limitations to this Study. The population represents a single company and may not be representative of the larger population of China. However, this focus is consistent with new models of knowledge discovery and health promotion among defined community populations – in this case, the urban working population. Additionally, longitudinal follow-up of a stable population has the advantage of allowing for insights into risk trajectories and outcomes. Second, participants are recruited from an annual health screening and so we lack information about employees who are eligible but do not participate in the health screening. However, very few employees decline participation; nonetheless, processes for collecting this information are being developed. Third, the collection of outcomes for any longitudinal study is a challenge. The current mechanisms, including self-report and claims data of services rendered through the Qingdao medical insurance bureau are already more advanced than most population-based studies. In the first year of attempting to obtain medical records, over half were successfully obtained. Further efforts are needed to improve this proportion, though this can be accomplished. Additionally, the ascertainment of claims data allows for extensive utilization and cost analyses, which are unique to this study.

China's unique position of being a low- to middle-income country with significant intellectual resources, as well as shared goals between academic, private, and public domains – can provide important lessons for the world on the effects of globalization, and the tools needed to protect the health of the public. Longitudinal, population-based studies play an important part in this learning. The Qingdao Port

Cardiovascular Health Study is designed to fill these knowledge gaps, and provide important insights for the public and health care system at large.

Legends

Figure 1. Examination Sites for the Qingdao Port Cardiovascular Health Study

Figure 2. Organizational structure of the Qingdao Port Cardiovascular Health Study

Figure 3. Distribution of Frequency of Study-Participant Follow-up

Figure 4. Distribution of New and Returning Study Participants per Year

Contributors: XJ, XL, JL, HMK and LJ led the protocol design; ESS and JL drafted the manuscript, assembled historical documents of study design and protocols, and reviewed processes for data collection; YW analyzed data and provided critical review of the manuscript; FAM, JAS, NSD, KN, HMK and JL provided critical review of the study design and manuscript.

Funding: This study was funded by the Qingdao Port Group and Fuwai Hospital, National Center for Cardiovascular Diseases

Competing Interests: None

Ethics approval: The study was approved by Qingdao Fuwai Hospital on Mar 1, 2013, and by Yale University on Dec 11, 2013. The trial was registered at ClinicalTrials.gov (NCT02329886) on Dec 20, 2014.

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Examination Sites for the Qingdao Port Cardiovascular Health Study
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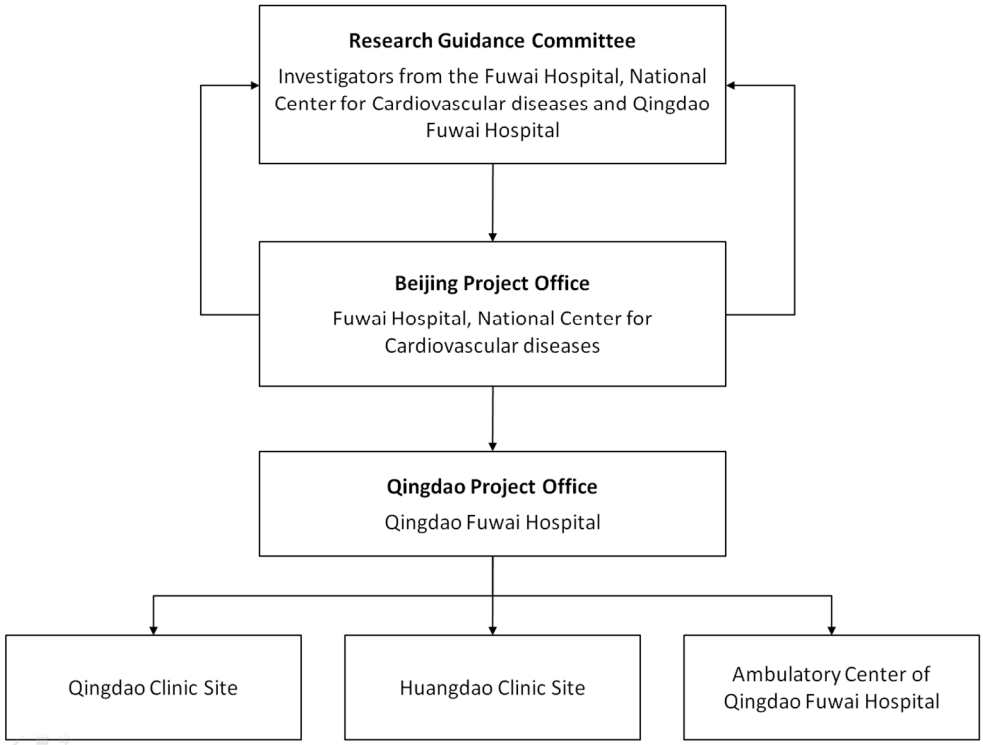

Organizational structure of the Qingdao Port Cardiovascular Health Study
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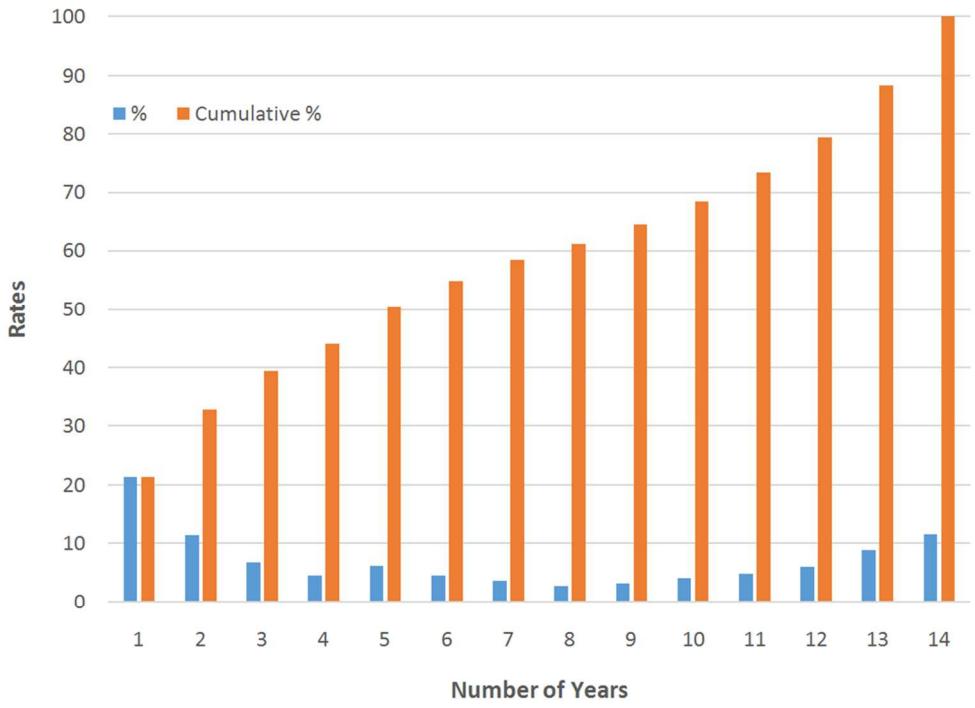

Distribution of Frequency of Study-Participant Follow-up
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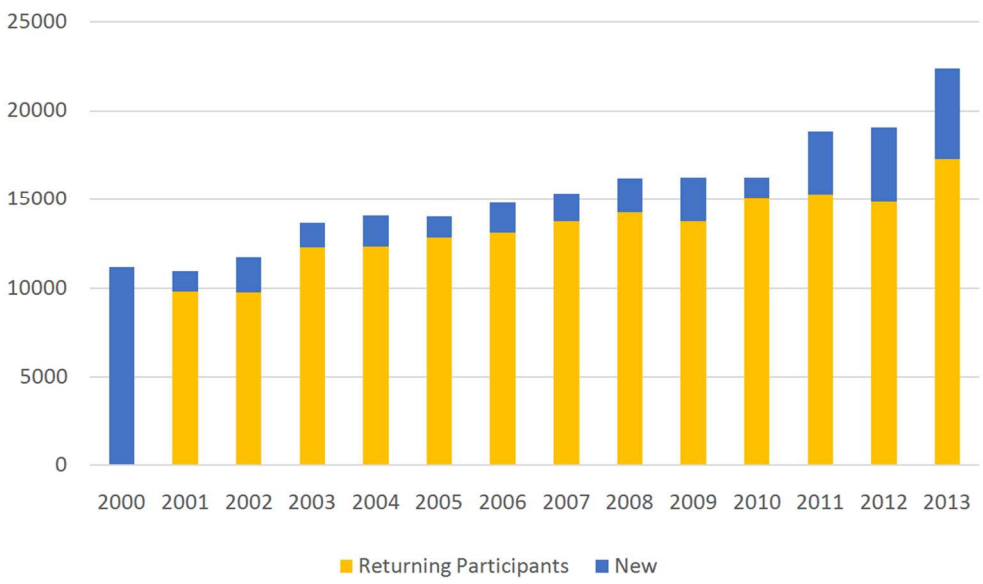

Distribution of New and Returning Study Participants per Year
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The Qingdao Port Cardiovascular Health Study

Consent Form

Name: _____ ID Number: _____ Employee ID:_____

Date of birth: _____Year ____Month ____Day Gender: ○ Male ○ Female

- I understand the objective and contents of the study. I understand the study does not involve any intervention to me.
- I have asked questions and these have been answered satisfactorily. I have had enough time to consider whether I will take part in the study.
- I understand that I have the opportunity to ask questions during the study at any time.
- I understand that my participation is voluntary and that I am not required to take part in the study and that I am free to quit at any time for any reason without my legal rights being affected. If I quit the study, I understand that I will not receive questionnaire surveys or provide bio-samples in the future.
- I understand I will receive questionnaire surveys and will give blood, urine and saliva bio-sample over the course of the study.
- I provide permission that my blood and urine samples be taken for long-term storage, and not be tested immediately. I agree to that these bio-samples can be tested for genetics and other kinds of analyses in the future. I understand these analyses are being conducted for medical research, and the results will be kept confidential.
- I understand that the information collected about me for this study will be kept secure and confidential. It will be stored on encrypted databases at Qingdao Fuwai Hospital and the National Center for Cardiovascular Diseases, Fuwai Hospital.
- I understand that authorized researchers from the research management committee may review sections of my medical records and other health related information. I give permission for these individuals to have access to my records on the understanding that this will be done in confidence.

I am delighted to take part in the Qingdao Port Cardiovascular Health Study

_____	_____	_____
Printed name of employee	Signature	Today's date
_____	_____	_____
Printed name of person providing consent	Signature	Today's date

Table 2. Overview of variables collected at health screening exams: 2000-2013

Domains	Variable Overview	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
	Cohort (n)	12023	11193	12884	14314	14335	14152	14857	15383	16322	16381	16378	19081	21319	23301
Demographics	Age, sex	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Education, Occupation	√	√	√	√										√
	Income				√										√
Health Behaviors	Smoking	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Alcohol Use	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Physical Activity	√	√												√
	Nutrition	√	√	√											√
	Reproductive History	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Family History	√	√	√	√	√	√		√	√	√	√	√	√	√
Medical History	High Blood Pressure	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Antihypertensive Medication	√		√	√	√	√	√	√	√	√	√	√ +	√ +	√ +
	Hyperlipidemia	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Hyperlipidemia Medication	√	√	√	√										√
	Diabetes	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Diabetes Medication	√	√	√	√	√	√	√	√	√	√	√	√ +	√ +	√ +
	Stroke	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Coronary Heart Disease	√	√	√	√										
	Angina, AMI				√	√	√	√	√	√	√	√	√	√	√
	Kidney Disease	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	COPD/Asthma	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Renal Disease				√	√	√	√	√	√	√	√	√	√	√

	Kidney Stones	√	√	√	√	√	√	√	√	√	√	√	√	√	
	Liver Disease	√	√	√	√	√	√	√	√	√	√	√	√	√	
	Thyroid Disease						√	√	√			√	√	√	
	Cancer														√
	PCI														√
	CABG														√
	Other Cardiac Surgery														√
	Gout					√	√	√	√	√	√	√	√	√	√
	Stroke or AMI Hospitalization	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Health Status, Sleep, Stress, Anxiety, Depression		√												√
Chinese Medicine Use		√	√	√	√	√	√	√	√	√	√	√	√	√	√
Quality of Life															√
Laboratory Analysis	Cell Blood Count							√	√	√	√	√	√		
	Triglyceride/Total Cholesterol	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	HDL and LDL							√	√	√	√	√	√	√	√
	Fasting glucose	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Creatinine	√	√			√	√	√	√	√	√	√	√	√	√
Physical Examination	Vital Signs; Anthropometrics	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Eye Exam					√	√	√	√	√	√				
	Cardiopulmonary Auscultation					√	√	√	√	√	√	√	√	√	√
	Liver/Spleen Palpation					√	√	√	√	√	√	√	√	√	√
	Thyroid					√	√	√	√	√	√				

	Palpation														
	Proctology Exam					√	√	√	√	√	√				
	Dental Exam			√	√	√									
ECG		√	√	√	√	√	√	√	√	√	√	√	√	√	√
Diagnostic Imaging	Chest X-ray	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Breast Infrared Image	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Uterine Ultrasound	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Liver/Gallbladder Ultrasound					√	√	√	√	√	√	√	√	√	√
	Carotid Ultrasound													√	√
	Thyroid Ultrasound										√	√	√	√	√
	Echocardiogram													√	√

√ + = Medication list abstracted

BMJ Open

Cohort profile: The Qingdao Port Cardiovascular Health Study: A Prospective Cohort Study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-008403.R1
Article Type:	Cohort profile
Date Submitted by the Author:	23-Jul-2015
Complete List of Authors:	Spatz, Erica; Yale University/Yale-New Haven Hospital, Center for Outcomes Research and Evaluation; Yale School of Medicine, Section of Cardiovascular Medicine Jiang, Xianyan; Qingdao Fuwai Hospital, Section of Cardiovascular Medicine Lu, Jiapeng; State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center of Cardiovascular Diseases Masoudi, Frederick; University of Colorado Anschutz Medical Campus, Division of Cardiology Spertus, John; Saint Luke's Mid America Heart Institute/University of Missouri-Kansas City, Health Outcomes Research Wang, Yongfei; Yale University/Yale-New Haven Hospital, Center for Outcomes Research and Evaluation; Yale School of Medicine, Section of Cardiovascular Medicine Li, Xi; State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center of Cardiovascular Diseases Downing, Nicholas; Yale University/Yale-New Haven Hospital, Center for Outcomes Research and Evaluation Nasir, Khurram; Baptist Health Medical Group, Division of Cardiology Du, Xue; State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center of Cardiovascular Diseases Li, Jing; State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center of Cardiovascular Diseases Krumholz, Harlan; Yale University/Yale-New Haven Hospital, Center for Outcomes Research and Evaluation; Yale School of Medicine, Section of Cardiovascular Medicine Liu, Xiancheng; Qingdao Fuwai Hospital, Jiang, Lixin; State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, National Clinical Research Center of Cardiovascular Diseases
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Secondary Subject Heading:	Epidemiology
Keywords:	population surveillance, cardiovascular diseases, longitudinal studies, cohort studies, outcomes research

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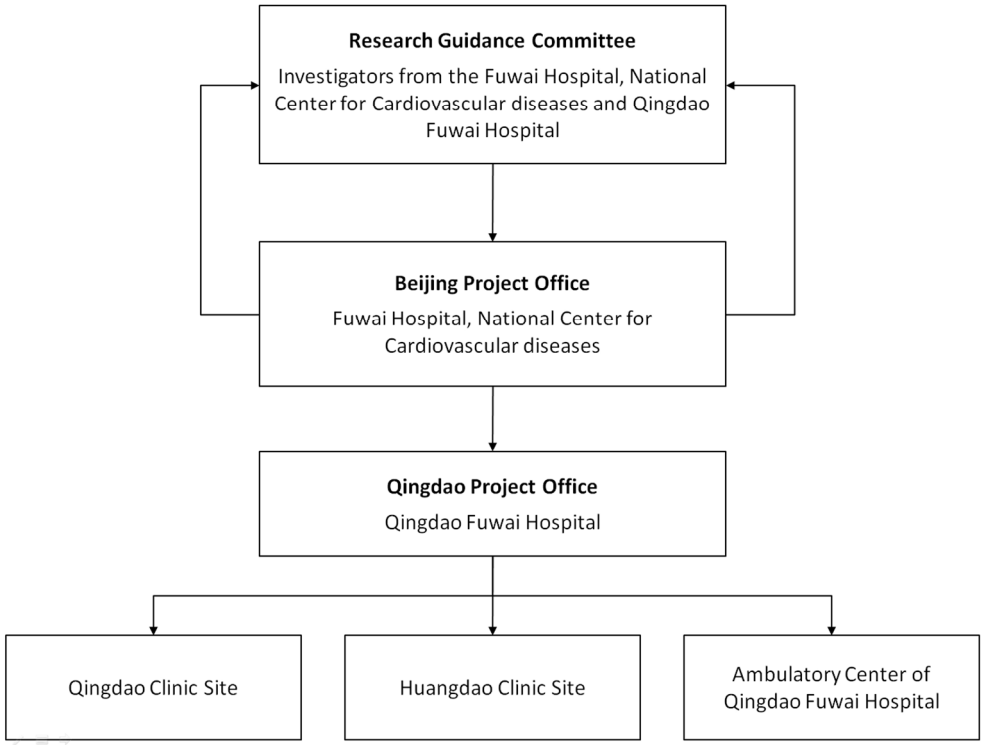

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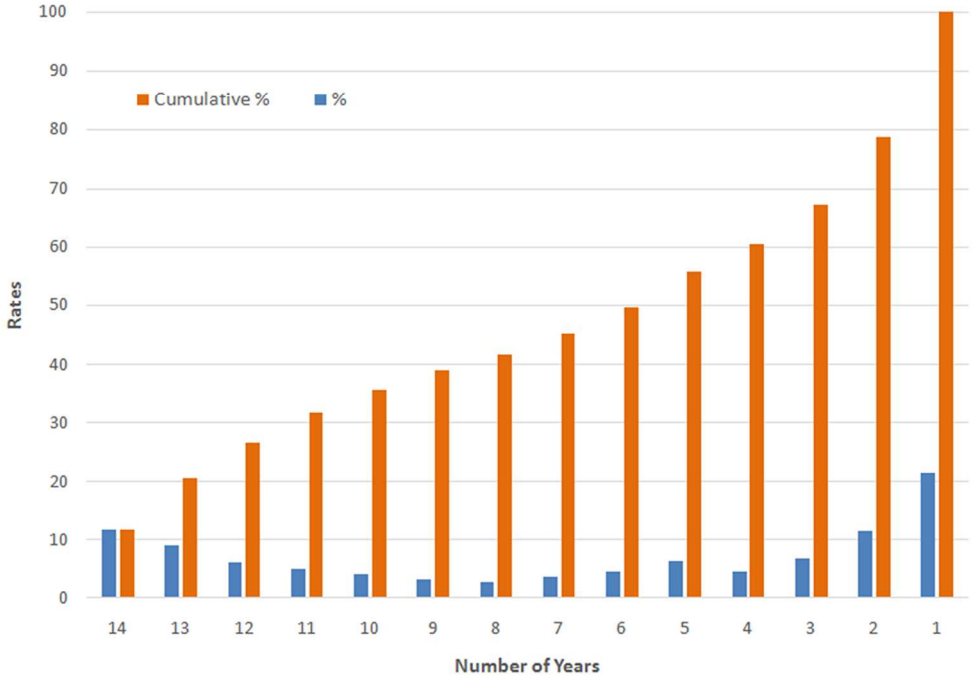

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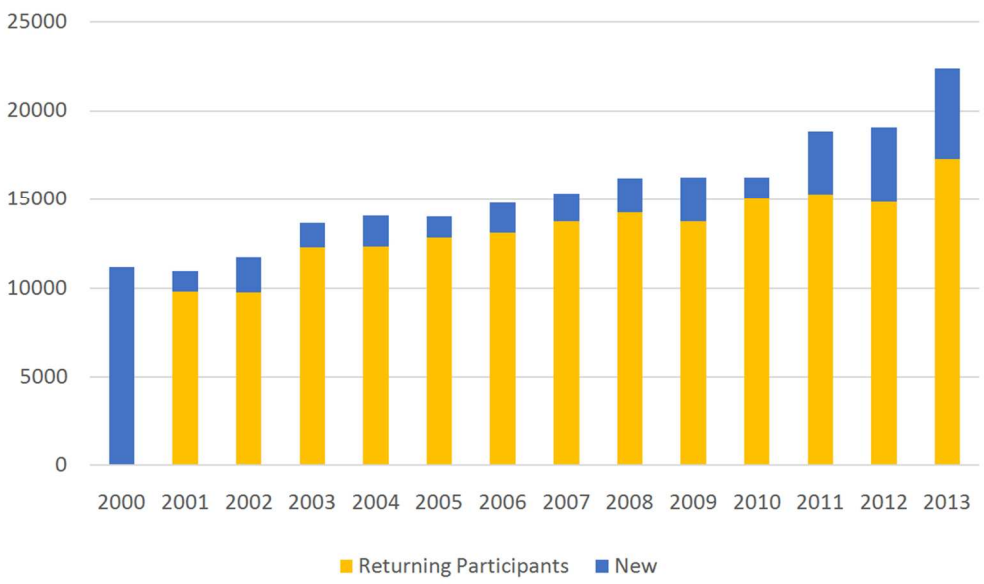

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	Physical Activity	√	√												√
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	Antihypertensive Medication	√		√	√	√	√	√	√	√	√	√	√ +	√ +	√ +
	Hyperlipidemia	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Hyperlipidemia Medication	√	√	√	√										√
	Diabetes	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Diabetes Medication	√	√	√	√	√	√	√	√	√	√	√	√ +	√ +	√ +
	Stroke	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Coronary Heart Disease	√	√	√	√										
	Angina, AMI				√	√	√	√	√	√	√	√	√	√	√
	Kidney Disease	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Liver Disease	√	√	√	√	√	√	√	√	√	√	√	√	√	
	PCI														√

BMJ Open

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Key Words: population surveillance; cardiovascular diseases; longitudinal studies; cohort studies; outcomes research

Word Count: 3,642

Abstract

Purpose: In China, efforts are underway to respond to rapidly increasing rates of heart disease and stroke. Yet the epidemiology of cardiovascular disease in China may be different from that of other populations. Thus, there is a critical need for population-based studies that provide insight into the risk factors, incidence, and outcomes of cardiovascular disease in China. The Qingdao Port Cardiovascular Health Study is designed to investigate the burden of cardiovascular disease and the socio-demographic, biological, environmental and clinical risk factors associated with disease onset and outcomes.

Participants: From 2000 through 2013, 32,404 employees aged 18 years or older were recruited from the Qingdao Port Group in China, contributing 221,923 annual health assessments. The mean age is 43.4 (SD 12.9) and 79% are male. Annual health assessments, governed by extensive quality control mechanisms, include a questionnaire (capturing demographic and employment information, medical history, medication use, health behaviors and health outcomes),physical examination, electrocardiography, and blood and urine analysis. Additional non-annual assessments include an x-ray, echocardiogram and carotid ultrasound; bio-samples are collected for future genetic and proteomic analyses. Cardiovascular outcomes are accessed via self-report and are actively being verified with medical insurance claims; efforts are underway to adjudicate outcomes with hospital medical records.

Findings to Date: Early findings reveal a significant increase in cardiovascular risk factors from 2000 to 2010 (hypertension: 26.4% to 39.4%; diabetes: 3.3% to 8.9%; hyperlipidemia: 5.0% to 33.6%; body mass index >28 m/kg^2: 14.1 to 18.6%).

Future Plans: We aim to generate novel insights about the epidemiology and outcomes of cardiovascular disease in China, with a specific emphasis on the potentially unique risk factor profiles of this Chinese population. Knowledge generated will be disseminated in the peer-reviewed literature, and will inform population-based strategies to improve cardiovascular health in China.

Trial Registration Number NCT02329886

Strengths and limitations of this study:

- This is a prospective cohort study has been conducted for above 10 years.
- The study collected a variety of information including cardiovascular risk factors, clinical outcomes and bio-samples, allowing a wide ranging assessment of risk factors and genetic factors related to cardiovascular disease onset and cardiovascular outcomes.
- Findings will have broad implications for China's workforce and for employer-based healthcare.
- Participants are limited to a single company and may not be representative of the larger population of China.

INTRODUCTION

Epidemiologic studies are the cornerstone for understanding cardiovascular risk factors and disease. Decades of research extending from the Framingham Heart Study and other cardiovascular studies (e.g., Atherosclerosis Risk in Communities Study) provide insight into the complex interplay between biology, behavior, environment, and genes on the risk of cardiovascular disease (CVD) and stroke.[1-4] However, existing studies of the epidemiology of CVD may have limited relevance to other populations, particularly in countries with different health behaviors and environments.

The relationships between risk factors and CVD outcomes differ between populations. As demonstrated in the World Health Organization Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, along with other studies, metabolic, dietary and other lifestyle factors do not consistently portend the same cardiovascular risk across populations.[5-11] The graded relationship between higher cholesterol levels and mortality from coronary heart disease varies among Western countries[12] and may differ in China.[13-14]Studies also demonstrate differences in the epidemiology of stroke, with the slope of the relationship between blood pressure and stroke steeper among Asian populations as compared with Australian populations,[15] and hemorrhagic stroke occurring more frequently in Chinese populations than in Western populations.[16] In summary, the epidemiology of heart disease and stroke in China, and its associated risk factors, may be different from that of other populations, and thus may have different implications for intervention and prognosis. Understanding potential differences in the epidemiology and outcomes of CVD in China requires population-based studies.

Well-conducted, population-based prospective studies focused on CVD are critical, especially as China is experiencing remarkable changes in the cardiovascular risk of its population.[17-20] Similar to other developing countries undergoing an epidemiologic transition, there has been a dramatic rise in the prevalence of non-communicable diseases such as CVD.[13 21]Approximately 1 in 5 Chinese adults aged 18 years or older(~230 million people) have CVD, the prevalence of which is expected to double in the next decade.[2223] Beyond the expected rise in CVD associated with longer life expectancy,[24] other factors such as urbanization,[25] environmental pollutants,[26-28] and sociocultural shifts[29] have been associated with the increasing prevalence of obesity,[30] hypertension,[31] diabetes,[32] and smoking,[33] though their relationship with CVD in China has not been well described.[34-35]To date, there are few contemporary, prospective, population-based studies to identify factors associated with heart disease and stroke in the Chinese population.[36-37]

Accordingly, the Qingdao Port Group and its affiliated hospital, Qingdao Fuwai Hospital, established the Qingdao Port Cardiovascular Health Study in 2000, a prospective cohort study of employees of the Group, with the aims of monitoring the incidence of CVD and associated risk factors and identifying risk factors associated with the incidence of CVD and cardiovascular outcomes. Knowledge gained from this study will be used to guide China's efforts in preventing and managing heart disease and stroke. In this paper we describe the design, cohort and investigational priorities of the Qingdao Port Cardiovascular Health Study.

COHORT DESCRIPTION

Study Design and Investigational Priorities

The Qingdao Port Cardiovascular Health Study was started in 2000. The study is designed to monitor CVD trends and to understand risk factors contributing to chronic conditions with a focus on heart disease and stroke.[38-39]Specifically, the main investigational priorities are: 1. Surveillance of cardiovascular risk factors, disease, and outcomes; 2.Investigation of socio-cultural, biological, behavioral, social, and environmental factors on work productivity, CVD onset and CVD health outcomes; 3.Development and validation of risk models to predict cardiovascular events; and 4. Genetic and proteomic analysis of biological samples to elucidate disease mechanisms and inherited risk profiles.

Setting, Recruitment and Eligibility

The Qingdao Port Group of the Shandong province in China is one of the oldest and largest shipping and trade companies in the world. (Figure 1) The workforce is diverse, with administrative personnel, technical personnel (e.g., pilots, computer analysts and information technology specialists, police, teachers, physicians, nurses and other hospitals staff), production operators, ship workers, dockworkers, and drivers. Among them, ship-and dock workers account for the majority of all staff.

The company contributes to each employee's health insurance plan, which is administered by the Qingdao medical insurance bureau. The plan covers annual health assessments, on-site ambulatory medical care, and coverage of inpatient services rendered at the Qingdao Fuwai Hospital, the local hospital and partner in this study, as well as other public hospitals in Qingdao city. All employees aged

18 years or older, who present for an annual health assessment, are eligible for Study participation. The only exclusion are workers who are migrant, as they are not covered by the local health insurance and do not receive annual health examinations, effectively excluding them from Study participation.

Prior to 2013, employees were verbally asked to participate. Since then, however, employees sign an informed consent document prior to enrollment. (Appendix 1: Translated informed consent document). Among the employees who present for a health assessment, almost all (98%) agree to participate in the Study. At each annual visit, employees renew their agreement to participate. Participants are informed that the data are confidential.

The annual health assessments, offered at the three work sites, serve as the platform for data collection. The organizational structure for the study is presented in Figure 2.

Health Assessment Components

Annual health assessments, which are performed by 35 trained physicians and nurses, consist of a questionnaire, physical examination, electrocardiography, laboratory testing, and bio-sampling. In 2013, echocardiography and carotid ultrasound were additionally performed and bio-samples were collected for future analysis. Currently, there are 466 unique variables summarized by domain in Appendix2.

1. Questionnaire

A standardized questionnaire is administered by trained personnel during a face-to-face annual health assessment (Appendix 3). Questions are adapted from prior epidemiologic studies,[40] and when available, questionnaires validated in Chinese are used.[41] The following domains are assessed: demographics (e.g., income, education, family structure); personal medical history (e.g., medical

history, medication use and adherence); family history; health behaviors (e.g., nutritional intake; physical activity[42]; smoking; alcohol use/abuse; health care utilization (e.g., hospitalizations; use of traditional Chinese medicine); menopause (including hormone use);emotional health (e.g., anxiety, stress); and employment structure (e.g., physical labor; shift-work).

2. Physical examination

A detailed, comprehensive physical examination is conducted at baseline by trained medical staff. Nurses measure height, weight, waist circumference, hip circumference, blood pressure, and heart rate. Physicians perform a detailed eye and ear exam, dental assessment, thyroid palpation, cardiopulmonary auscultation, and abdominal examination. Nurses and physicians follow standardized protocols for measurement and examination. Height (cm), weight (kg), and waste and hip circumferences are measured using sonographic technology (Ultrasound Height & Weight Machine, TCS-160D-W/H, Shenzhen Sonka Electronic Techology Co., Ltd, Guangdong, China),averaged to the nearest 0.1 unit. Instruments are calibrated weekly with phantom mannequins. Blood pressure and heart rate are measured after the patient has been seated for 5 minutes using a calibrated electronic sphygmomanometer. Blood pressure measurement is performed by placing the cuff on the dominant arm, at the level of the heart, and taking the average of three measurements spaced one minute apart. Heart rate is recorded contemporaneously with each blood pressure measurement.

3. Laboratory tests

Venipuncture, performed by trained nurses, is obtained annually. Some blood chemistries are repeated each year (e.g., fasting glucose, lipid profile, creatinine). Tests performed intermittently include: liver function and thyroid function.

4. Bio-samples for future analysis

Since 2013, participants are invited to submit bio-samples, including blood, urine and saliva samples, for storage and future DNA, RNA and biochemical analysis. Over 90% of Study participants have consented to date. Whole blood samples are drawn into EDTA, serum gel, heparin lithium, and Tempus blood RNA tubes (Applied Biosystems, Foster City, California, USA) for future gene expression analysis. When stored in Tempus tubes at −80°C, the whole blood RNA retains high integrity and purity for over a six year period.[43] To collect saliva, participants are asked to chew a cotton roll for 45 seconds; the cotton roll is placed into a Salivette® tube (Sarstedt AG & Co, Nümbrecht, Germany). Within 24hours, trained nurses centrifuge blood and saliva samples and divide and transfer the samples into cryovials, according to standard protocols. Urine is transferred directly into cryovials. All samples are immediately stored at -80℃, and are transported to Fuwai Hospital, NCCD for long-term storage within two months.

5. Additional testing

Electrocardiography is performed every year. Additionally, specific cardiovascular screening tests were conducted during different years including: chest x-ray, echocardiogram and carotid ultrasound. All imaging tests are conducted by certified technologists in accordance with standards set forth by the Ministry of Health.

Follow-up

Follow-up health assessments are performed annually. While the employee population is dynamic, among the 32,404 study participants from 2000-2013, more than half (18,111; 55.9%) have 5 or more years of follow-up; 11,537 (35.6%) participants have 10 or more years of follow-up. (Figure 3) Of the

original cohort of 11,201 people that started in 2000, 7,433 were not participating in annual follow-up as of 2013. For example, among 22,128 study participants who enrolled between 2000 and 2010, 3280 (14.8%) had no follow-up visit after 2011 and before the end of the 2013 measurement period. These employees may have left the company or declined further participation; it is also possible, though less likely, that they missed 3 consecutive visits and will return in 2014. Distinguishing individuals with interrupted visits from permanent drop-outs is a goal for the future (Table 1).

Table1. Follow-up among Study Participants

Description	Total Cohort	Returning Participants	Non-returning Participants	
			N	%
2000 to 2001-2013	11201	11201	0	0.00
2000-2001 to 2002-2013	12363	12260	103	0.83
2000-2002 to 2003-2013	13474	13291	183	1.36
2000-2003 to 2004-2013	15849	15212	637	4.02
2000-2005 to 2006-2013	16614	15637	977	5.88
2000-2006 to 2007-2013	17136	15838	1298	7.57
2000-2007 to 2008-2013	17963	16263	1700	9.46
2000-2008 to 2009-2013	18947	16833	2114	11.16
2000-2009 to 2010-2013	20221	17476	2745	13.57
2000-2010 to 2011-2013	22128	18848	3280	14.82
2000-2011 to 2012-2013	22670	18775	3895	17.18
2000-2012 to 2013	24636	18521	6115	24.82

The components of the follow-up visit are the same as the baseline assessment and include a face-to-face interview, physical examination, laboratory testing and imaging exams specified for that year. New participants are recruited each year (Figure 4) and, since 2003, participants are followed into retirement, up until death. In China, the statutory retirement age for general workers is 60 years for men and 50-55 years for women, depending on their job position. Among heavy laborers, the retirement age is 55 years for men and 45 years for women. Senior professionals may work until the age of 65-70 years. Since 2003, retirees account for approximately one-quarter of all annual health assessments each year, with approximately 7,000 retirees in the study.

Outcomes

The following cardiovascular outcomes are collected: unstable angina; acute myocardial infarction; revascularization with either percutaneous coronary intervention or coronary artery bypass grafting; heart failure; stroke; and all-cause death. As part of the annual health questionnaire, participants are asked to report information on newly diagnosed diseases, hospitalizations, and treatments that occurred in the previous year. Self-reported health outcomes are actively being linked with medical claims data; since all employees have the same insurance plan, complete insurance claims data are available for all years except 2000 and 2001, years in which not all employees were insured with the same plan. Additionally, since 2013, medical claims are linked with health assessment data every 3 months, independent of whether participants self-reported a clinical outcome. From the medical claims, the following information is abstracted: admission date, discharge date, discharge diagnoses and corresponding International Classification of Disease (ICD) codes; and discharge status. Deaths are monitored by the insurance plan and shared with the Qingdao Port Company and Study group, which prompts the collection of death certificates and autopsy reports to elucidate the cause of death.

Hospital medical records are also assessed to verify cause of death. In the case that hospitalization records or other supportive records are not available, interviews with the person's relatives and physicians are conducted to acquire the date and cause of death.

Efforts are underway to adjudicate a subset of outcomes using hospital medical records. In 2013, 855 participants reported hospitalizations, 300 of which were reported to have occurred at Qingdao Fuwai hospital, all of which were verified. Among patients who reported being hospitalized outside of Qingdao Fuwai Hospital (n=555), medical records from 246 participants were obtained. These records came directly from participants, though there are efforts to develop a process that will enable the direct collection of Study participants' medical records from outside hospitals. Consistent with other cardiovascular research protocols,[44] adjudicators will review the clinical diagnosis and the claims-based ICD code, and compare with self-reported data. Discrepancies between the medical record and claims data are resolved by the research guidance committee in Fuwai Hospital, NCCD.

Quality Assurance and Control

All research staffs participate in a 2-dayintensive training focused on administering the questionnaire and learning the protocols for blood pressure measurements, anthropometry, blood collection and sample processing, electrocardiography and data entry. Further operational training is conducted at the study sites. Each year, all equipment, including the biochemical analyzer, ultrasound machine, x ray machine, electronic sphygmomanometer and ultrasound stadiometers are tested and calibrated by the Qingdao Institute of Measurement and Testing and the Qingdao Institute of Weighing Apparatus Management; annual calibration certificates by these two institutes are required. The validity of all measurements is checked monthly by examination of data outliers and missing fields. Additionally, site

monitoring is conducted by two trained research staff from Fuwai Hospital, NCCD every 3-6 months, assessing: (1) the completeness of the documentation and (2) fidelity to protocol for recruitment, health screening, physical examination and sample collection and processing. Finally, annual meetings are held to discuss problems with measurement and data entry and to optimize study processes.

To improve the validity and reliability of the measurement of cardiovascular risk factors, questions were adapted from prior epidemiologic studies in China, such as questions assessing smoking and dietary patterns.[40] In 2013, questionnaires that were previously validated in Chinese were incorporated. We used the Alcohol Use Disorders Identification Test (AUDIT) questionnaire to identify persons with hazardous and harmful patterns of alcohol consumption from,[41] the International Physical Activity Questionnaire (IPAQ) to assess physical activity[42] and the EuroQoL (EQ-5D) to measure health status.[45]

The definition of hyperlipidemia changed from earlier years in accordance with the level of data available. For example, in some prior years, no blood lipid tests were performed; in these years, only self-report and medication use were used to define hyperlipidemia. Since 2010, hyperlipidemia is defined as: either self-report of high cholesterol or dyslipidemia (either: total cholesterol ≥5.2mmol/L or low-density lipoprotein ≥3.4 mmol/L or high-density lipoprotein <1.0 mmol/L or triglycerides≥1.7mmol/L) or use of a lipid lowering medication.

From 2000-2012, data were collected on paper and double-entered by two different researchers into a computer-based system to reduce error. Since 2013, results from the questionnaire, physical examination, laboratory testing and other examinations are collected electronically with an Internet-based data management system developed specifically for the study. To increase the validity and reliability of the data, this system included predefined data formats, predetermined data ranges for

quantitative data, and required fields. After research personnel enter the data, internal data checks are performed to confirm that the data are correctly entered. Finally, prior to the beginning of each measurement year, all personal information is verified (name, sex, ID number, work ID, company, department, contact telephone number and address); these steps improve the accuracy of participants' information, decrease the duration of face-to face interview time and facilitate linkage with medical insurance records.

Data Security and Management

All data are treated as protected health information and are securely stored in an encrypted and password-protected database. Laptops are password-protected, and all research personnel have individual passwords to log-in to the system. All data between the three sites are independent, which means research personnel only have access to the data collected at their own site.

All source data, including questionnaires, health assessment results, hospitalization and clinical medical records, are securely stored in the 3 clinic sites of the Qingdao Fuwai Hospital. The electronic version of the files as well as the image files of electrocardiograms and chest x-rays are securely stored on the servers of Qingdao Fuwai Hospital. The Research Guidance Committee, comprised of investigators from the Fuwai Hospital, NCCD and the Qingdao Fuwai Hospital, make the ultimate decisions on the usage of the data governed by institutional review board approval.

Cohort

From 2000 through 2013, a total of 32,404 study participants contributed 221,923 health assessments. In this cohort, the mean age is 43.4 (SD 12.9) and 79% were male, consistent with the demographics of

the company. Participants ranged in occupation: loading/unloading (9.7%); warehouse clerk (8.0%); ship crew (18.8%); other shipping and dockworkers (29.9%); management (19.9%); other (13.7%).

Findings to Date

Table 2 compares cardiovascular risk factors across three time periods (2000 to 2005 to 2010), demonstrating an increased prevalence of hypertension (26.4% to 38.6% to 39.4%) and diabetes (3.3% to 5.9% to 8.9%). The 2005 estimates for hypertension and diabetes are similar to those observed in the 2005 International Collaborative Study of CVD in Asia (InterAsia).[46] Rates of hyperlipidemia increased from 5% to 12.4% to 33.6% across Study years; however, full blood lipid panels were not conducted between 2001 and 2006. These rates are lower than those observed in a meta-analysis in which 41% of community-residing adults had dyslipidemia.[47]

Table 2. Trends in Characteristics of Study Participants (2000 to 2010)

Description	2000		2005		2010	
	n	%	n	%	n	%
Total Participants	12023		14152		16378	
Retirees	NA	NA	3369	23.8	4594	28.1
Demographics						
Age (Mean; SD)	39	8.7	45	12.0	45	13.7
Gender						
Male	9227	76.7	10945	77.3	13076	79.8
Female	2796	23.3	3207	22.7	3302	20.2
Cardiovascular Profile						
High Blood Pressure*						
Yes	3176	26.4	5457	38.6	6451	39.4
Missing	0	0	4	<0.1	4	<0.1
Diabetes†						
Yes	396	3.3	838	5.9	1458	8.9
Missing	0	0	0	0	4	<0.1
Hyperlipidemia‡						
Yes	600	5.0	1749	12.4	5499	33.6‡

Missing	0	0	565	4.0	4	<0.1
Acute Myocardial Infarction						
Yes	NA	NA	66	0.5	128	0.8
			50	0.4	301	1.8
Stroke						
Yes	66	0.5	130	0.9	188	1.1
Missing	3	<0.1	49	0.4	320	2.0
Anthropometrics						
Waist (cm)						
Mean (SD)	81.6	11.2	83.9	9.6	86.6	12.3
Missing	0	0	292	2.1	215	1.3
BMI (cm/kg^2)§						
Missing	25	0.2	277	2.0	190	1.2
Normal body weight (<24)	5852	48.7	5317	37.6	6313	38.6
Overweight (24to<28)	4456	37.1	5972	42.2	6831	41.7
Obese (≥28)	1690	14.1	2586	18.3	3044	18.6
Systolic Blood Pressure						
Missing	0	0	58	0.4	63	0.4
Mean (SD)	121	17.1	122	18.3	125	20.9
Diastolic Blood Pressure						
Mean (SD)	80	12.1	82	11.6	82	11.2

*Self-report or mean blood pressure >=140 systolic or >=90 mmHg diastolic or antihypertensive medication therapy
†Self-report or fasting glucose >=7.0 mmol/L or glucose lowering medication
‡Self-report or lipid lowering therapy for year 2000; self-report only for year 2005; self-report or dyslipidemia (either: total cholesterol ≥5.2mmol/L or low-density lipoprotein ≥3.4 mmol/L or high-density lipoprotein <1.0 mmol/L or triglycerides≥1.7mmol/L) or lipid lowering medication therapy for year 2010
NA: not available; SD: standard deviation.

Strengths and Limitations

The Qingdao Port Cardiovascular Health Study is uniquely positioned to measure disease incidence and trends, characterize the complex relationships between biology, environment, culture, and behavior with disease onset, trajectories and outcomes, and ultimately inform the approach to CVD prevention and population health, especially among China's urban, working population. Knowledge generated from the population of the Qingdao Port Cardiovascular Health Study will have broad implications for

China's workforce and for employer-based healthcare, wherein large employers contract with health systems to provide comprehensive health care services to its employees, including health screenings, outpatient medical care and inpatient services. In 2006, approximately 160 million people (about 28% of the urban population) were covered by employer-based health insurance.[48] This Study, which aligns research objectives with current health challenges, is embedded in the employer-based health services model, and can thereby foster knowledge dissemination and translation among such employers. Importantly, the rigorous methodological design and health data collection, follow-up into retirement, and linkage of health screening data with insurance claims and medical records, will provide a rich opportunity to investigate disease trajectories and outcomes and inform approaches to population-based healthcare delivery. Other Chinese population-based studies, such as the China National Diabetes and Metabolic Disorders Study (2007–2008), while nationally representative, are cross-sectional and less comprehensive.[18 47] The Singapore Chinese Health Study[49] and the Chinese Health and Retirement Longitudinal Study (CHARLS)[50] provide data on older populations, though they are not focused on CVD and have limited follow-up data. To date, there are no longitudinal, population-based cardiovascular studies of the urban, working population of China. The Study is supported by the Fuwai Hospital, NCCD– a clinical research group with longstanding expertise in standardized data abstraction, cataloguing, and linkage, ensuring excellent quality control and organization for scientific investigation.[51-53]

There are some limitations to this Study. The population represents a single company and may not be representative of the larger population of China. Additionally, employed individuals may be healthier than the general population, which may influence the relationship between risk factors and disease onset. However, the study subjects from the Qingdao Port Company are from diverse sectors of the

workplace; moreover, the dataset is rich with health behaviors and socioeconomic information which may account for variation in associations within the population. The focus on an employee population is consistent with new models of knowledge discovery and health promotion[54]. Additionally, longitudinal follow-up of a stable population has the advantage of allowing for insights into risk trajectories and outcomes. Second, participants are recruited from an annual health screening and so we lack information about employees who are eligible but do not participate in the health screening. However, very few employees decline participation; nonetheless, processes for collecting this information are being developed. Related to this, it is possible that in some cases, responses to the interview questions might be influenced by the participants' perceptions that their answers might affect their employment status. Third, the collection of outcomes for any longitudinal study is a challenge. The current mechanisms, including self-report and claims data of services rendered through the Qingdao medical insurance bureau are already more advanced than most population-based studies. In the first year of attempting to obtain medical records, over half were successfully obtained. Further efforts are needed to improve this proportion, though this can be accomplished. Additionally, the ascertainment of claims data allows for extensive utilization and cost analyses, which are unique to this study.

Collaboration

The Qingdao Port Cardiovascular Study is ongoing, with increasing capacity to adjudicate cardiovascular outcomes, enhancing self-reported outcomes with insurance claims data and hospital medical records. The publications committee and data analytic center are comprised of researchers from the National Center for Cardiovascular Disease of the Fuwai Hospital, Beijing and from Yale

University – two institutions with a longstanding partnership and commitment to improving cardiovascular health in China. At this time, all research will be conducted in collaboration with the Study investigators. Prospective collaborators are encouraged to contact either Jiapeng Lu (jiapeng.lu@fwoxford.org) or Erica Spatz (Erica.spatz@yale.edu).

China's unique position of being a low- to middle-income country with significant intellectual resources, as well as shared goals between academic, private, and public domains – can provide important lessons for the world on the effects of globalization, and the tools needed to protect the health of the public. Longitudinal, population-based studies play an important part in this learning. The Qingdao Port Cardiovascular Health Study is designed to fill these knowledge gaps, and provide important insights for the public and health care system at large.

Further Details

Ethics Approval: The ethics committees of the Qingdao Fuwai Hospital and the Fuwai Hospital, NCCD (Mar 1, 2013), and Yale University (Dec 11, 2013) approved the study. The trial was registered at ClinicalTrials.gov (NCT02329886) on Dec 20, 2014.

Author Contributions: XJ, XL, JL, HMK and LJ led the protocol design; ESS and JL drafted the manuscript, assembled historical documents of study design and protocols, and reviewed processes for data collection; YW analyzed data and provided critical review of the manuscript; FAM, JAS, NSD, KN, HMK and JL provided critical review of the study design and manuscript.

Funding: This study was funded by the Qingdao Port Group and Fuwai Hospital, National Center for Cardiovascular Disease

Competing Interests: No, there are no competing interests.

Acknowledgments: We would like to thank Dr. Bingnan Zhang, MD, MBA for her assistance with the translation of documents and contributions to the manuscript.

Data sharing: No additional data available

Legends

Figure 1. Examination Sites for the Qingdao Port Cardiovascular Health Study

Figure 2. Organizational structure of the Qingdao Port Cardiovascular Health Study

Figure 3. Distribution of Frequency of Study-Participant Follow-up

Figure 4. Distribution of New and Returning Study Participants per Year

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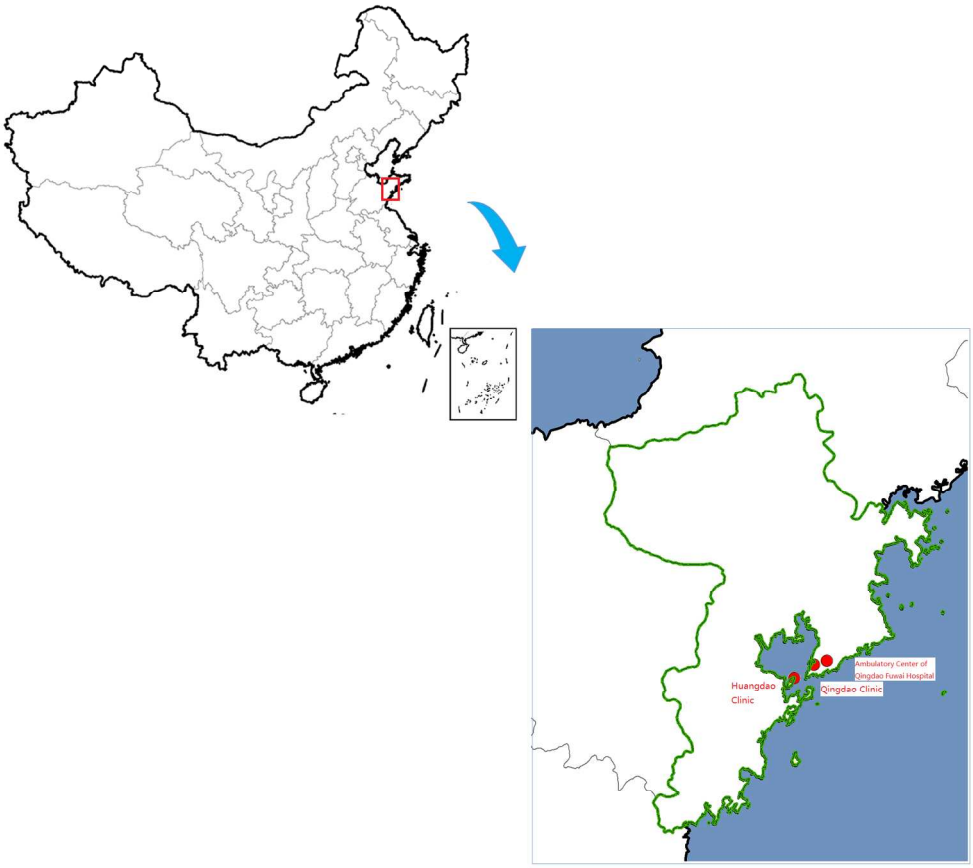
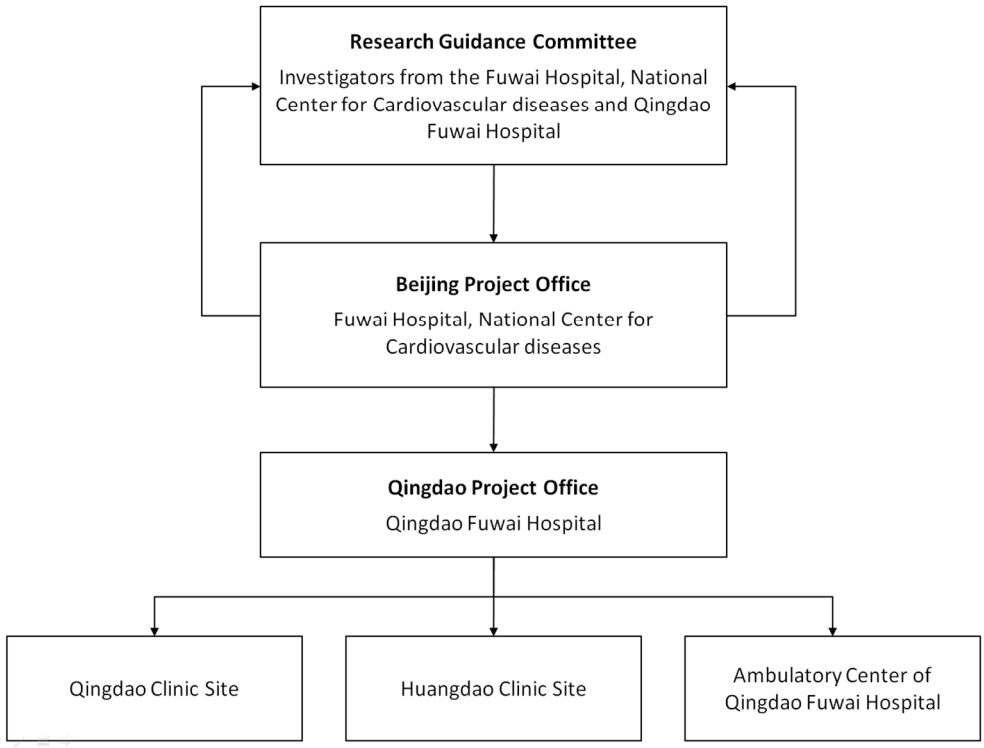
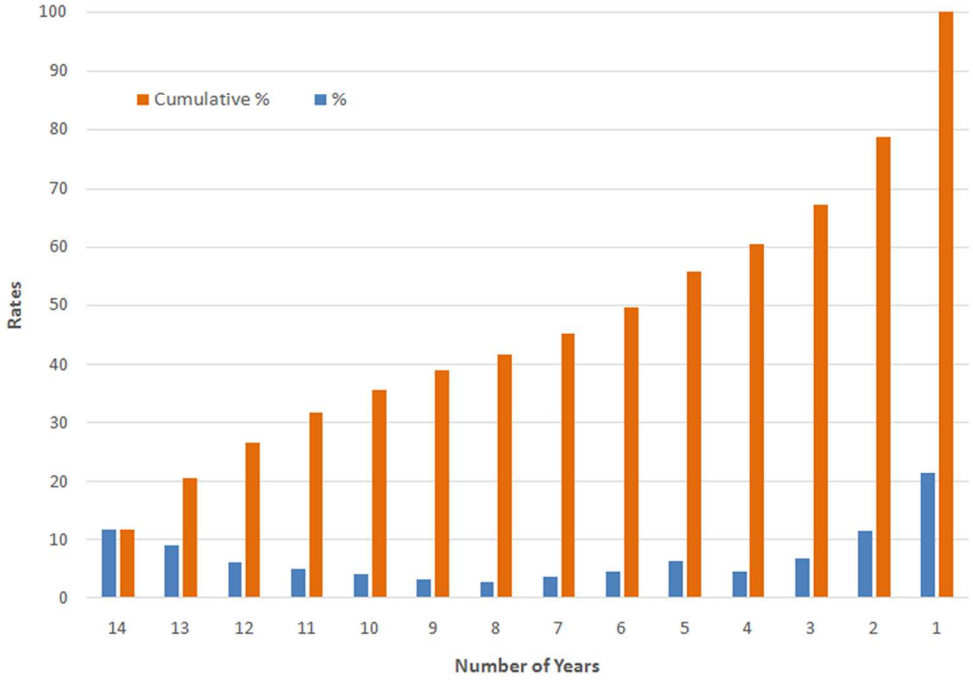


Figure 1. Examination Sites for the Qingdao Port Cardiovascular Health Study
577x518mm (96 x 96 DPI)



375x279mm (300 x 300 DPI)



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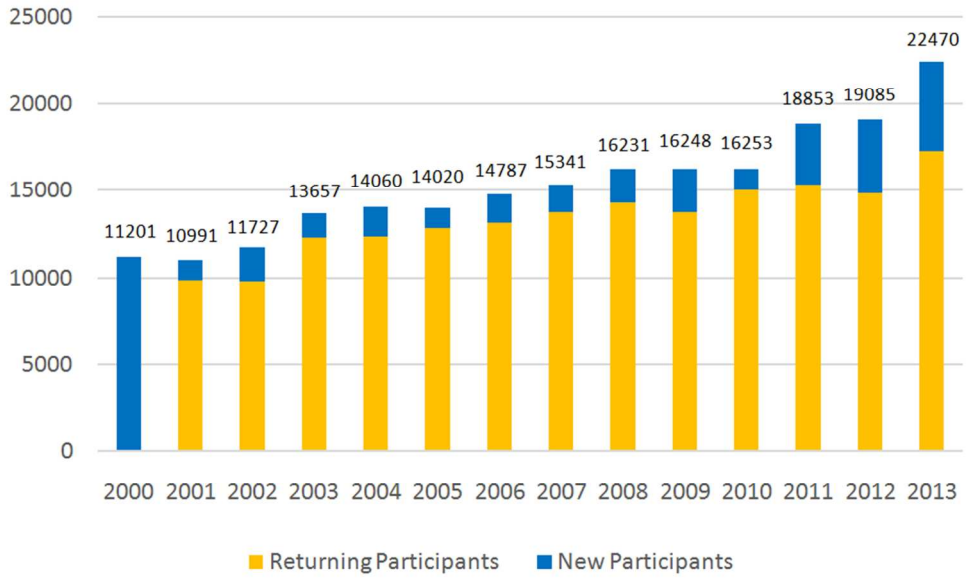

Figure 4. Distribution of New and Returning Study Participants per Year
250x147mm (300 x 300 DPI)

Table 2. Overview of variables collected at health screening exams: 2000-2013

Domains	Variable Overview	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
	Cohort (n)	12023	11193	12884	14314	14335	14152	14857	15383	16322	16381	16378	19081	21319	23301
Demographics	Age, sex	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Education, Occupation	√	√	√	√										√
	Income				√										√
Health Behaviors	Smoking	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Alcohol Use	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Physical Activity	√	√												√
	Nutrition	√	√	√											√
	Reproductive History	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Family History	√	√	√	√	√	√		√	√	√	√	√	√	√
Medical History	High Blood Pressure	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Antihypertensive Medication	√		√	√	√	√	√	√	√	√	√	√ +	√ +	√ +
	Hyperlipidemia	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Hyperlipidemia Medication	√	√	√	√										√
	Diabetes	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Diabetes Medication	√	√	√	√	√	√	√	√	√	√	√	√ +	√ +	√ +
	Stroke	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Coronary Heart Disease	√	√	√	√										
	Angina, AMI				√	√	√	√	√	√	√	√	√	√	√
	Kidney Disease	√	√	√	√	√	√	√	√	√	√	√	√	√	√
	Liver Disease	√	√	√	√	√	√	√	√	√	√	√	√	√	
	PCI														√