

Mini-Review of the Chin-Shan Community Cardiovascular Cohort Study in Population Health Research in Taiwan

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Preventing and controlling non-communicable diseases (NCDs) is a growing global public health concern, and evidence-based data from population-based health studies are needed in order to develop appropriate public health policies for controlling NCDs. The Chin-Shan Community Cardiovascular Cohort (CCCC) study is a prospective cohort consisting of participants from one community in China in 1990-1991, and has provided substantial evidence-based data on domestic and global health issues in preventive cardiology fields. The present study is a mini-review of the CCCC study. In this review, we have described the historical background of the cardiovascular disease burden and related risk factors, especially lifestyle factors, subclinical disease markers, biomarkers and prediction models, and related international collaborative projects. In addition, this mini-review study provides a measure of insight into future plans for 21st century epidemiological research in cardiovascular diseases, suggesting possible areas of focus for future research.

Key Words: Cardiovascular diseases • Population-based study • Risk factors

INTRODUCTION

The prevention and control of non-communicable diseases (NCDs) are a growing public health concern globally. The Global NCD Action Plan 2013-2025 of the World Health Organization (WHO) has established a target of 25% relative reduction in NCD mortality by 2025, a plan otherwise known as the “25×25” strategy.¹ To evaluate the prevalence, incidence and mortality of coronary heart disease, stroke and chronic lung disease in Taiwan, we need to understand the current vital statistics and behavioral and biological risk factors of these NCDs, including community-based epidemiology. In addition, novel biomarkers and subclinical disease mea-

surements have been applied to predict the risk of NCD occurrence and prevention. Therefore, adopting a systematic approach for conducting a longitudinal population-based cohort study provides an ideal experimental scenario by which to evaluate the NCD risk factor burden.

Current evidence and guidelines for cardiovascular disease prevention and control have originated from various randomized clinical trial data and observational population-based cohort studies. In addition, population-based studies provide a real-world scenario and exposes the actual management and control measures applied to health-related problems. However, most of the available information related to NCD has been collected from western countries and specific geographic and cultural factors may potentially confound the associations and disease trends of cardiovascular disease. For example, in Asian-Pacific countries, stroke is reported to be more prevalent than coronary heart disease, and the prevalence of metabolic syndrome is also higher among Asian-Pacific populations than among Caucasian populations. Therefore, evidence from domestic data, which

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emphasizes the unique characteristics of the Taiwan population and differences compared with western populations,^{2,3} is likely to provide more substantial support for the national government in developing appropriate health policy.

The Chin-Shan Community Cardiovascular Cohort (CCCC) study is a prospective cohort study that collected data systematically during the years 1990 and 1991 from participants over age 35 years of age who inhabited the Chin-Shan community. The main purpose of the present mini-review was to describe the protocol and study design of the CCCC, as well as examine the behavioral and biological risk factors for NCDs.

BACKGROUND: HISTORY OF THE CCCC STUDY DESIGN

The original idea of the CCCC study was unique.⁴ Professor Yuan-Teh Lee conducted this study, leading the faculty of the Division of Cardiology, Department of Internal Medicine, National Taiwan University, through the use of various facilitating resources, including the National Science Council, Department of Health and the Foundation of Taiwan Electricity Company. This study began in 1990 by recruiting 1703 men and 1899 women at least 35 years of age and older, with homogeneous Chinese ethnicity, and living in the Chin-Shan township 30 km north of metropolitan Taipei, Taiwan. The participants' anthropometric and lifestyle data, medical history and current health conditions were assessed by interview questionnaires in 2-year cycles, and the validity and reproducibility of the collected data and measurements have been reported elsewhere in detail.⁴ Through the assistance of trained young faculty and medical students, we added to the original 3602 participants by collecting various questionnaires addressing basic lifestyle and behavioral information along with medical histories, clinical evaluation and physical examinations. At first, we measured the carotid artery intima media thickness and echocardiographic profiles in a systematic way. More recently, we further developed the bi-annual examination format to collect morbidity and mortality data according the following strategy: first, we surveyed the hospitalization and outpatient service records corresponding to the questionnaires; second, we regularly

collected the death certificate documents from the local health station and performed oral interviews with relatives and family members about death events to confirm the causes of death. The chronological description of this cohort is shown in Figure 1.

ACHIEVEMENTS

As a result of conducting extensive surveys and continuously collecting data, this CCCC study has made several contributions to population health, especially in preventive cardiology fields (Table 1).

Epidemiological data for cardiovascular disease and related risk factor survey

We examined risk factor distribution and the associated atherosclerosis outcome studies. For example, we investigated metabolic syndrome, hyperglycemia and diabetes risk for the atherosclerotic events,⁵ and fasting and post-challenge 2-hour hyperglycemia and insulin resistance status indicators for coronary artery disease risk.⁶ In addition, we found that hyperuricemia was associated with a risk of developing type 2 diabetes, instead of metabolic syndrome effect.⁷ Hyperlipidemia has also played an important role in atherosclerosis events. Furthermore, the various roles of lipid components may have differential effects on coronary heart disease. We found that apolipoprotein B and non-HDL cholesterol concentrations were more important than

Year	Stage	Activity
1990-1991	Initiation	Collecting baseline data
1992-1995	Extension	Comprehensive data collection
1995-2000	Development	Events follow up and ascertainment
2000-2008	Progressing	2003: Hold collection due to SARS 2005: Chin-Shan Hospital Inauguration
2008-2015	Upgrading	2010.10.1: Hospital affiliated to NTUH
2015	Translational research	Omics & novel biomarker study International cooperation

Figure 1. The chronological description for the Chin-Shan Community Cardiovascular Cohort study, Taiwan.

Table 1. The listed achievements from the Chin-Shan Community Cardiovascular Cohort Study, Taiwan

Achievements	Description
Epidemiological data for disease and related risk factor survey	Prevalence and incidence rates of diseases and risk factors
Lifestyle and behavioral factors and their roles in health	Tobacco smoking, dietary habits, physical activity and sleep habits
Subclinical disease markers	Carotid artery intima thickness and plaque, echocardiographically measured parameters
Novel biomarkers	Homocysteine, C-reactive protein, fatty acids, Vitamin D, Omics-based biomarkers
Prediction models for NCD risk	Point-based prediction models for various cardiovascular outcomes
Novel biostatistical methodological approaches	Life-course epidemiology Partial least square-structure equation model High-order interaction model Kappa for multiple raters Time-dependent covariate model
Domestic and international collaborations	Dietary intervention, PROG-IMT project, EchoNormal, and CHARGE-FORCE consortiums

other lipid components in the risk of coronary artery disease.⁸ In addition, lipoprotein (a), an intriguing and unique lipid component related to coagulation and atherosclerosis, was also investigated through the cross-sectional study and prospective cohort study of CCCC.^{9,10} A modest relationship was found between lipoprotein (a) and atherosclerotic risk; however, the association for incident risk existed only in participants whose lipoprotein (a) was in the 90th percentile.

Atrial fibrillation has been considered a great disease burden because of its high prevalence among elderly individuals and consequent stroke risk. The CCCC findings showed significant risk for stroke among participants with atrial fibrillation.¹¹ In addition, through our cooperation with Dr. Lip, we stratified the risk of stroke and bleeding using available scores to compare the validity and predictive value of these scores.

The roles of lifestyle and behavioral factors in health

Second, we investigated participants' lifestyle habits, including physical activity,¹² sleep habits, and sodium intake associated with the risk of diabetes, hypertension and cardiovascular events. Regarding sodium intake, we showed clearly that urinary sodium excretion was significantly associated with the risk of hypertension,¹³ and that actual sodium intake was still higher than the recommended intake.

Subclinical disease markers

Subclinical disease markers were investigated th-

rough the CCCC study, including carotid intima media thickness and carotid plaque status as well as left ventricular mass and echocardiographically-measured parameters. These subclinical disease markers can be considered surrogate markers for the atherosclerotic burden, and provide additional predictive value for predicting cardiovascular risk. In addition, they can be applied to identify and screen individuals at middle and high-risk. Through extensive cohort survey, we found that carotid intima media thickness and plaque severity were related to the risk of developing coronary heart disease and stroke.¹⁴ In addition, left ventricular mass, aortic dimension and left atrial dimension indeed play independent roles in the risk of cardiovascular events.¹⁵⁻¹⁷ We also found that carotid intima media thickness has a dose-response relationship to blood pressure magnitude,¹⁸ and we have provided the normal range of carotid intima media thickness in the general population.¹⁹ In addition, carotid intima media thickness and plaque status provided additional predictive value for the risk of coronary artery disease and stroke, after controlling for traditional risk factors.¹⁴

Novel biomarkers

Novel biomarker data, including for homocysteine, vitamin D and fatty acids, were measured from the stored serum/plasma samples of the CCCC study participants. Through the measurements of various biomarkers, we have provided substantial evidence for the roles of these biomarkers in the risk of atherosclerosis.

For example, Dr. Sun and colleagues²⁰ examined the role of homocysteine in the risk of stroke and all-cause mortality. In addition, vitamin D concentrations were associated with cardiovascular death in CCCC participants.²⁰ Moreover, various fatty acids measured by gas chromatography, including saturated fat, polyunsaturated fatty acids, and trans-fat are noted for their roles in further cardiovascular risk.²¹ Recently, we have joined an international cooperative effort to investigate the roles of various fatty acids for the risk of diabetes and cardiovascular events, and will contribute our data for global health problem-solving. In addition, using urine biomarker profiles, Dr. Lin applied a nested case control study design using a subset of the CCCC cohort to investigate the oxidative and nitrosative stress and the risk for incident stroke.²²

Constructing various prediction models for NCD risk

We provided the simple points-based manual score prediction models for various atherosclerotic risk outcomes, including type 2 diabetes,²³ hypertension,²⁴ chronic kidney disease,²⁵ stroke,²⁶ and coronary heart disease.²⁷ We also provided clinically measured variables, in addition to biochemical variables, for identifying and screening individuals at a high risk for further events.

Novel biostatistical approaches

We applied novel biostatistical approaches to investigate disease outcomes. For example, we used the kappa measures and cluster analysis approach to examine the consistency of various diagnostic criteria of metabolic syndrome.²⁸ In addition, we used the latent growth curve model from the life course epidemiology approach to investigate the roles of repeated measures of blood pressure and low density lipoprotein cholesterol for the carotid intima media thickness values.²⁹ Moreover, we used the partial least square structure equation model to incorporate various metabolic syndrome indicators for the risk of left ventricular mass values among study participants;³⁰ this method conquers the problem of multi-collinearity among various related factors. In addition, we used the multi-dimensional reduction approach for high-order interaction effects to focus on the various obesity indicators, metabolic syndrome, Framingham risk score, and the risk of

non-alcoholic fatty liver status from participants who underwent health examinations in the hospital.³¹ In addition, we used time-dependent covariate models to investigate the roles of repeated uric acid concentrations for cardiovascular events, which was an appropriate way to address the variable patterns of exposure on outcome status.³²

Domestic and international collaborations based on the CCCC study

Domestic cooperation with experts in various medical professional disciplines, including neurologists, ophthalmologists, clinical pathologists, orthopedists, nutritionists, and public health fields, was an important achievement for this study. Through cooperation with professionals of different backgrounds, we were able to provide training courses and learning platforms for young medical students and faculty, and supplied the data for hypothesis testing and idea exploration.

International cooperation during this cohort study included involvement in the Emerging Risk Factors Collaboration for carotid intima media thickness data (PROG-IMT project),³³ and for echocardiographic data (EchoNormal, The Echocardiographic Normal Ranges Meta-Analysis of the Left Heart Study)³⁴ and the Expert Group in Metabolic Risks on the Global Burdens of Disease, Risk Factors and Injury. Recently, we contributed CCCC fatty acids data into the CHARGE-FORCE consortiums to evaluate the roles of fatty acids in the risk of cardiovascular events and type 2 diabetes.

UNIQUENESS, INNOVATION AND BREAK THROUGH OF THE CCCC STUDY

Due to long-term follow-up of participants, the CCCC study can be considered as a platform to provide evidence-based health research and policy reference for cardiovascular disease prevention and control. Biologically, the process of atherosclerosis is a universal phenomenon; however, specific ethnic populations and geographical areas confounded the process significantly due to differences in genetic, cultural, lifestyle and environmental factors. Therefore, providing evidence-based data from this community-based cohort is valuable for understanding the specific patterns of cardiovascular

diseases and related risk factors. Additionally, these data will help health policy makers provide feasible strategies to promote improved health.

FUTURE PLANS: 21st CENTURY EPIDEMIOLOGICAL RESEARCH IN CARDIOVASCULAR EPIDEMIOLOGY FIELDS

Beginning on Oct. 15, 2005, the forerunner of the Chin-Shan Branch of National Taiwan University Hospital was launched in the community as a symbol of the achievement of the CCCC study, and to provide a universal healthcare system for the people dwelling in and around the community. Affiliated with National Taiwan University Hospital since Oct. 1, 2010, the healthcare system is a milestone in providing primary prevention and health care and is promoted by leaders within the community. The community is thus empowered by this common sense health promotion plan, especially in primary prevention of lifestyle-related factors to ultimately reduce the disease burden.

In the future, there are several important platforms should be available for young researchers. First, new opportunities must be provided for young investigators and collaborations with experts for sharing strategies for data analysis. Second, training programs must be developed for young investigators to allow them to explore various hypotheses in cardiovascular disease issues in applying high-quality data. Third, a network must be developed for research activities, including a regular journal club/seminar, an interactive network with outside experts for brainstorming, regular debate and discussion, statistical support, as well as available mentorship and workshop training activities. Finally, it is important to provide critiques for observational studies in chronic disease fields, including causation issues, with limited budget restrictions to allow ongoing research to be maintained.

From the perspective of public health and academic research, certain important issues must still be taken into consideration and prioritized. These priorities include the need to investigate chronic disease health issues derived from primary health promotion, followed by secondary health screening and management. Additionally, there must be rehabilitation and handicap limi-

tation to achieve integrated health care service. It furthermore is essential to use up-to-date information technology and social media network platforms to promote health education and management, and use cost-effective methods (such as electronic health data or technology-based information data from patients) to reduce the cost of research and create specific sub-cohorts based on specific populations in order to study specific biomarkers and clinical measurements. Also, it is beneficial to apply state-of-the-art medical technology for early screening and diagnosis as well as treatment and prognosis. It is also necessary to establish a platform for translational research, integrating various types of information such as images, biomarkers, "omics"-based data (genomics, proteomics) and clinical measurements. Finally, it is also valuable that the overall general health of the population is promoted to better spotlight population health through research and social activities.

CONCLUSIONS

In summary, the health promotion and health policy contributions of the CCCC study are several and important, in part to establish the hospital as a health center for individuals dwelling around the community; second, to provide evidence-based health data regarding the distribution of chronic diseases and related risk factors; and third, to improve overall health status in the population after community intervention performed via screening high-risk individuals and conducting lifestyle and dietary interventions.

Furthermore, the CCCC study needs to extend the following tasks to facilitate population-based health study in Taiwan: first, to facilitate education training programs; second, to extend the research direction in a new era of preventive cardiology; third, to cooperate with international and domestic research experts; and finally, to influence public health policy making in Taiwan.

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